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TWENTIETH CENTURY

PRACTICE

AN INTERNATIONAL ENCYCLOPEDIA

OF

MODERN MEDICAL SCIENCE

BY

LEADING AUTHORITIES OF EUROPE AND AMERICA

EDITED BY

THOMAS L. STEDMAN, M.D.

NEW YORK CITY

IN TWENTY-ONE VOLUMES

VOLUME XXI

SUPPLEMENT

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PREFACE

ALTHOUGH but two years have elapsed since the completion of this encyclopedia, the advances in certain lines of medical work have been so marked as to justify the preparation of a supplementary volume. The discovery of the Roentgen rays was made while the earlier volumes were in course of publication, and already the diagnostic and therapeutic applications of this form of radioactivity call for discussion in any treatise on general medicine or surgery. The demonstration, by officers of the United States Army in Havana, of the agency of the mosquito in the transmission of yellow fever, and the practical application of this demonstration to the suppression of the endemic focus of the disease in Cuba, have necessitated a restatement of the accepted teachings concerning yellow fever. The experience of medical men in the Far East has proved beyond question that the term dysentery covers at least two diseases, more or less alike in symptoms, but entirely dissimilar in causation, and so the need of an article on bacillary dysentery was apparent. The nature of cancer, whether or not it is of parasitic origin, is a subject of vital present interest, and it was therefore believed that a review of the work thus far done in the search for a tangible cause would be found timely. Hæmatology, including cytodiagnosis, is another subject in which progress has been so rapid as to demand a fresh presentation. All these topics and others have received authoritative treatment in this volume.

In thanking the many contributors to the original work for their prompt response to his request for a revision of their articles, so far as such might be necessary, and the several others who have written new treatises, the editor must crave pardon for having sometimes laid a heavy hand on their work. It was found after the printing of the book had been begun that the limits of one volume would be largely exceeded unless some pruning were done, and the bibliographies and historical sections were omitted as being the least essential parts. Those whom it was possible to advise of this necessity were graciously acquiescent, and the editor can but hope that others at a distance who could not be notified will be likewise indulgent. Those among the readers who regard a bibliography as a useful appendix to a scientific article must blame the editor and not the writers for its omission.

T. L. S.

NEW YORK, November 10th, 1902.

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THE ROENTGEN RAYS IN MEDICINE.

BY

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NEW YORK.

SCARCELY six years have elapsed since the Roentgen rays were discovered in the modest town on the Main, and many doctrines formerly regarded as incontrovertible have since been completely changed. It is significant that the progress of our pathological knowledge has altered many clinical pictures and in extending our diagnostic horizon has simplified our therapy. In the better understanding of numerous pathological processes a revolutionary change has taken place, and it is gratifying to note that with the clearing up of the anatomical conditions by the miraculous rays, the ratio between therapy and pathological knowledge has been altered by a great increase in the latter. It is an old dictum that the largest number of medicaments is recommended for those ailments which are least understood. The clearer the understanding becomes of the genesis and the anatomical relations of a pathological condition, the more the manifold therapeutic methods shrink into a few simple principles which in fact could be written on a finger nail, like the classic prescriptions of our great medical ancestor.

The proofs of the great usefulness of the rays in surgery as well as in medicine are now overwhelming. The recognition of foreign bodies in the remotest corner of the living organism is a matter of the greatest ease. Fractures and dislocations are shown as they really are in life. Accuracy takes the place of ignorance and doubt, and painful manipulations cease to be necessary for diagnostic purposes. Even the most skilful experts in fractures are unable to deny that there is a large number of bone injuries, the character of which could formerly not be recognized, on account of the swelling of the area involved or of the obscurity of the symptoms. The number of cases of fracture formerly mistaken for contusion or distortion was enormous. It is in such cases that a simple glance with the fluoroscope furnishes the most precise evidence. Whether there is comminution or impaction, or the intervention of muscular tissue or intraarticular fracture

or combination with a dislocation, can be at once clearly determined. If the picture be fixed on a photographic plate, the nature of the injury can be studied at leisure, and the proper line of treatment easily decided upon without subjecting the patient to any tentative manipulations. After a dressing is applied, the skiagram shows whether the fragments are in proper position. In fact, the execution of all therapeutic measures can be verified throughout the course of treatment by the skiagram, the dressing itself, even if consisting of plaster-of-Paris, offering no obstacle to the rays.

If the therapy proves to be imperfect, the rays show the nature of the condition. It is easily determined, for instance, whether an ankylosis is fibrous or osseous; and, consequently, the question whether the breaking up of adhesions or resection is indicated is settled at once.

It is needless to call attention to the frequent importance of a skiagraphic proof in court, for the protection of the surgeon as well as of the patient.

The knowledge of the various diseases of bones has been much augmented, and new laws of differentiation between inflammatory, syphilitic, tuberculous, or osteomyelitic processes, and osteoma, osteosarcoma, and osseous cyst have been established. The presence of concretions in the urinary and biliary tracts can be demonstrated.

In internal medicine the rays are also more and more appreciated to their full value. For the expert they prove to be of incalculable service in the diagnosis of many obscure ailments.

If it is only realized that most of the diseases of the thoracic organs can be represented, as, for instance, pleurisy, pyothorax, pneumothorax, lung abscess, tuberculous foci and cavities, and emphysema, and the relations of the heart and of the aorta, aneurysms, mediastinal tumors, and arteriosclerosis can be thoroughly studied, the immense importance of the rays for internal medicine is at once apparent.

Apparatus.

Apparatus Required for the Production of the Roentgen Rays.—The Roentgen rays are projected by an electric current from a platinum disc, included in a highly exhausted glass tube, which is opposite the negative electrode, or cathode (see Fig. 1).

To produce the necessary excitation in the exhausted tube (vacuum tube or Roentgen tube) an electric current is required. But the electric current generally used in an electric-lighting circuit would not be powerful enough to jump across the space of air left in a Roentgen tube. The ordinary electric-lighting current, as it is used for incandescent lamps, is of low pressure or "voltage" (generally 120 volts) and of a large rate of flow or "ampères." The current for the excita-

tion of a Roentgen tube requires a high voltage and an extremely low ampèrage. Therefore a transformation is necessary. In other words, transformation from a current of high intensity and low tension into one of less strength and high tension must be made. This is accomplished by means of a transformation apparatus, which may be in the form of a simple induction coil (Ruhmkorff coil) or a Tesla or high-tension induction coil, or by means of a static machine.

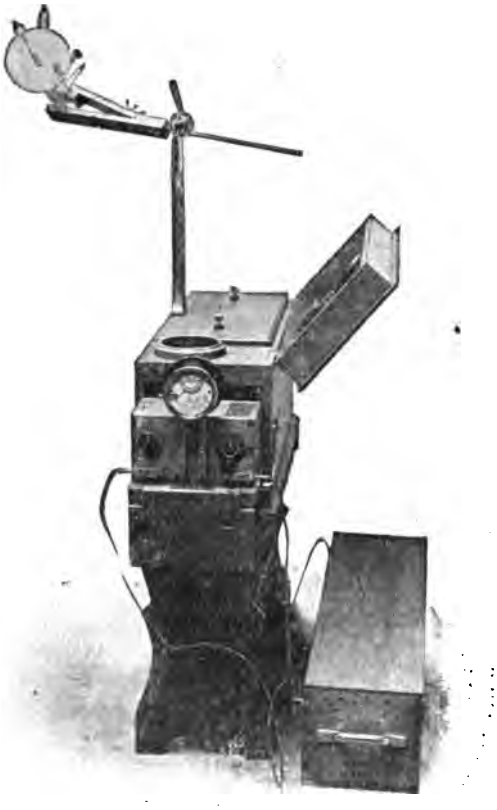


FIG. 1.—Portable Roentgen-ray Outfit, with Platinum Interrupter.

The three essential mechanisms therefore are:

1. The source of the current (the exciting apparatus).

2. The transformer, which converts the electric energy, furnished by the exciting apparatus, into a form suitable to the Roentgen tube.

3. The Roentgen tube, in which the electric energy is transformed into Roentgen rays. Some additional apparatus, such as stands, fluoroscope, and photographic appliances, the utilization of which will be considered below, is also necessary.

The Exciting and Transforming Apparatus.—The most efficacious transformation mechanism has proven to be the Ruhmkorff induction coil, which can be excited by means of a current derived either from a battery (Fig. 1) or from a so-called direct current (city supply).

A suitable battery, which furnishes a steady current, is the so-called Edison-Lalande cell battery. For use when travelling, storage batteries may be preferred, the great trouble, however, being that if they become exhausted at a distance from a city, they cannot be recharged, while the Edison-Lalande cells can be recharged anywhere.

The direct current is, of course, far superior to any other, since

there is neither charging nor supervising necessary, and not the least of its advantages is that it never embarrasses the operator by proving to be inefficient. Accordingly, whenever possible, connection with the 110- or 120-volt direct current should be made.

The stronger the coils the more efficacious the rays, as a rule. While good skiagraphs of the hand, forearm, etc., can be obtained by a small apparatus that gives a spark of the length of only six inches, in general large coils of a spark length of fourteen to fifteen inches are to be preferred. An inductor of this power, with a 110-volt direct current, should afford a current strength of from 1 to 2 ampères.

A Ruhmkorff induction coil consists of the core, the primary and secondary coil, the terminals of the secondary coil, a condenser, a contact breaker (electrolytic interrupter, vibrator, or air-brake wheel), and a rheostat (or shunt board). The core consists of a cylindrical bundle of soft iron wires which are firmly bound together. To secure proper insulation the core is soaked in shellac or paraffin. In order to insure quick demagnetization, and especially to prevent heating effects, the wires should have as small a diameter as possible. Upon this insulated core the primary coil, which consists of two layers of coarse copper wire, is wound. After it is covered with a tube consisting of many layers of paraffined paper or of hard rubber, the secondary coil is carefully wound upon it. The diameter of the wire for the secondary coil, which is generally wound with cotton or silk, is also small. Each layer must also be insulated with either shellac or paraffin. Many thousands of turns are required. The terminals of the wire connect with two binding posts containing two freely sliding rods.

In the interior of the coil a *condenser*, made of sheets of tinfoil, is placed. This makes the interruptions of the current more sudden, thus increasing the length of the spark. If the coil is used in connection with a battery, a contact breaker must be adjusted which, by quickly making and breaking the current passing through the primary coil, controls the periodicity of the vibration. If the coil is attached to the direct current, the air-brake wheel can be used, which renders the use of a "vibrating armature" unnecessary. The air-brake wheel attachment permits great rapidity of change in the electric circuit, thus intensifying the electromotive force in the secondary coil. It consists of two toothed wheels, the projections of which are brought into close contact with two flat brushes, which lead the current in and out, while the dentated wheels are rotated at a high speed by a small motor. This motor runs a pressure blower at the same time, the air blast from which is directed to a two-forked tube, through which it is led out again by two flat nozzles placed directly above the brushes. There the spark is blown out by the air blast as soon as it forms.

The question of the reliability of the interrupter is a very impor-

tant one. A poor interrupter jeopardizes the whole induction coil, which in view of its high price is no small matter. There are reports from clinics, in which the simple Wagner interrupter attached to an old induction coil required an ampèrage of 22 in order to produce an effective light. Such apparatus is soon burned out. Recently the electrolytic interrupter has come into favor (Fig. 2). The current passing through the coil is controlled by a rheostat. By combining this with the air-brake wheel the electromotive force on the secondary coil is augmented more than it would be with a simple motor apparatus controlled by a shunt-board. The Wehnelt interrupter increases

FIG. 2.—Electrolytic Interrupter with Three Electrodes.

the intensity of the bombardment by producing a powerful secondary discharge. A platinum wire projects from the sealed end of a glass tube and dips into a ten-per-cent. aqueous solution of sulphuric acid. Besides this a lead plate is immersed in the liquid through which the electric current is sent.

The *alternating current* requires more complicated apparatus, so that its handling presupposes the experience of an electrician.

While the various kinds of induction coils and transformers represent what is generally known as current or dynamic electricity, the *static machine* represents electricity at rest. In a coil the induction results from the variation of currents, which flow in the adjacent conductors. In a static machine the induction effects are created by the opposite and like electricities attracting and repelling each other. While the coils need a continuous supply of current, the static machine requires only an initial charge of electricity which is imparted as the result of friction. It is the static machine which represents the

most perfect mechanical means for creating a rapid and continuous succession of electric discharges.

A static machine, best adapted for Roentgen-ray work, is one in which a high mode of motion is developed and the current is developed at high speed. Of course the faster the apparatus is run, the more current is generated. Some of the modern static machines can be revolved as frequently as three thousand times a minute. The advantage of a static machine is that it requires no cells or chemical action. Still, for good skiagraphic work it must also be connected with a motor. Under favorable circumstances splendid skiagraphic work can be done with it, but it condenses moisture which affects its reliability. The temperature also influences it. In running a static machine care must be taken to separate the sliding-pole pieces about eight inches, to unscrew the large balls from the pole ends, and to remove the Leyden jars. The condensers must then be screwed on and the square platinum disc attached to the positive pole of the condenser. The length of the spark gap should be regulated so as to suit the vacuum; it must be long if the tube has a low vacuum, and be short if it has a high one. The machine must never be run backward or with wrong poles. Static machines, however, require tubes with a special vacuum.

The *Roentgen tube* (see Fig. 1) consists of a glass vessel, usually of an oblong or globular shape, from which the air is exhausted and into which the ends of electrodes are fused. With suitable exhaust pumps the rarefaction of the air in the tube can be brought as high as one-millionth part of the ordinary density. One of the electrodes ends in a disc of globular concave shape, which is made of aluminum; this electrode is called the cathode. The other ends in a disc of flat shape, which is of platinum; this is called the anode. The anode is situated opposite the cathode at an angle of about forty-five degrees. Its shape may be circular as well as square. Almost all of the modern tubes contain a second anode, which is connected with the main anode (platinum).

One of the great difficulties encountered in the use of the tubes is due to their soon becoming inefficient on account of the permanent change of pressure that occurs within them. In view of this variation of pressure, tubes have been constructed that permit lowering and raising of the vacuum within them at will. Siemens found that the fluorescing air forms dense bodies with the vapors of phosphorus, iodine, and other similar substances, thereby diminishing the pressure within the tube. On the other hand, if the walls of the tube are warmed, the stratum of air that condenses on the glass surface is driven away, thereby intensifying the pressure. In utilizing this principle, tubes with adjustable vacuum have been constructed which are provided with an adjuster shortening the space between the spark rods.

If currents of very high intensity are used, the platinum disc of almost all tubes becomes white hot after a short time, often after a few seconds, and if it is kept glowing a little longer, the platinum melts. To obviate this most embarrassing occurrence, tubes have recently been constructed in which the metallic parts are very thick and resistant. Such tubes permit of a current of maximum intensity for about one minute; then the very marked outlines of the picture become less distinct, the tube filling with blue light at the same time, which indicates that it is overheated; the current must then be turned off without delay. Such tubes make a good skiagraph of the thorax, for instance in forty-five seconds. Grunmach has constructed tubes that permit the glowing metal to be cooled by the intratubal circulation of a stream of cold water.

The best tubes are undoubtedly those which, when new, show a red-hot focus at the platinum disc while a low current is employed. New tubes that show fluorescence only when a high current is used should be rejected. It is one of the main characteristics of a good tube that it stands intense glowing of the platinum disc without being impaired at once; in other words, that it stands currents of high intensity. A good tube must also furnish a uniform light.

The variety of tubes manufactured now in various parts of the world is very great. The best are made in Thüringen, Germany. It requires a vast amount of experience and repeated experimentation to select tubes suitable for the particular apparatus to be employed. So it must be considered that static machines require tubes with a special vacuum, while tubes prepared for a battery set generally do not give satisfaction with an air-brake wheel apparatus or a Wehnelt interrupter, which permits the use of tubes of the highest vacuum obtainable at present. Tubes must be carefully studied, individualized, so to speak, just as different patients are to be judged differently, although suffering from the same disease.

The *vacuum* of the tubes is generally increased during their use, which necessitates a proportional increase of the intensity of the current. Therefore, even for inductors furnishing a very long spark, tubes with a low vacuum should be chosen, as the latter increases so much during use that at last the full power of the apparatus is required for producing an efficient light. Finally, however, the fluorescence of the tube ceases, even if the high current is employed. Then the vacuum can be reduced by heating the tube with an alcohol lamp, while a weak current is used, until the fluorescence becomes distinct again. If this fails, the tube should be surrounded evenly and tightly by gauze compresses slightly moistened with water.

At last, of course, all these procedures will prove to be without avail. Some tubes regain their efficiency simply by being left un-

touched for a few weeks, but finally they all become useless for diagnostic purposes. Then the resistance of the tube becomes so great that, while the interior hardly shows any fluorescence, most of the sparks go around the external surface. The presence of purple or red light points to a leak, which naturally renders the tube inefficient. Leaky tubes may be repaired by sealing the defect.

FIG. 3.—Dislocated Tuberculous Knee. Exposure with an extremely hard tube, showing no outlines.

The tubes must be preserved in a closet in which there is a uniform medium temperature. They should rest on padded shelves. Dust, which in the course of time always becomes adherent to the tube while in use, is to be wiped off by passing the dry palm of the hand gently over it.

Recently tubes have been constructed by Gundelach which permit of regulation by the diffusion of hydrogen. Into the wall of a tube of this kind a small palladium wire is fused, the end of which protrudes outside to the extent of two inches. If this protruding piece of palladium is heated by an alcohol lamp, the hydrogen of the flame diffuses into the interior of the tube, thus augmenting the intratubal vacuum. The heating process must be kept up for two seconds. The handling of these tubes is somewhat troublesome, but their usefulness is great.

The intensity of the rays increases in proportion to the height of the vacuum. If very high vacua are used, even the bones of the hand may become so translucent that they can hardly be distinguished on the plate. Thus it will be understood why, for the representation of the bones of the hand, a tube with a low vacuum (so-called soft tube) is to be chosen, while if the rays must permeate a very thick body, such, for instance, as the pelvis of a fat person, it is the high

vacuum tube (hard tube) only that would be capable of throwing so much light through it as to show a well-defined shadow on the plate. From this we learn that, according to the thickness and permeability of the object to be skiagraphed, tubes of low, medium, high, and very high vacuum must be at hand.

The degree of the intensity of the tubal light and the amount of penetration can be measured by a *skiameter*, various kinds of which have been devised. The principle consists in the attachment of small squares of tinfoil, of various thicknesses, to a fluorescing screen. The difference of thickness is indicated by little figures made of lead, which appear more or less distinct according to the thickness of their corresponding tinfoil. The author has found it useful to construct a skiameter consisting of fifty staniol discs, according to the number of knobs on his rheostat. To each disc a number, made of wire, is attached, which indicates the number of the staniol lamellæ. No. 1, for instance, contains one lamella only; while No. 50 contains fifty. That number which just permits of the recognition of the shadow of its wire cipher indicates the degree of intensity of the tube.

An experienced operator, however, tests the character of his tube by simply holding his own hand before the fluorescing screen. In fact, the hand is a better indicator than any artificial skiameter, as it contains many types of bones, from the massive carpal end of the radius to the delicate third phalanx of the little finger.

FIG. 4.—The same as Figs. 3 and 5. Exposure with a tube of medium hardness, showing the texture of the bone, the medulla, and the tuberculous foci.

As above mentioned, it is desirable to distinguish hard and soft tubes from those of medium hardness. If a tube shows the bones of the operator light gray and translucent, it is of excessive hardness, the contrasts are insignificant then, and the tube is fit only for the repre-

sentation of metallic bodies. Fig. 3 illustrates the indistinct skiagraph of a tuberculous knee-joint of a boy of four years, taken with a very hard tube.

A tube of medium hardness shows the bones of the operator's wrist, especially the lower radial epiphysis, grayish-black, but the structures appear still well defined. A tube of this kind is especially fit for the representation of thick bones, and of concretions. The picture from such a tube, which shows the bony structure and also the tuberculous foci of bone, is illustrated in Fig. 4.

FIG. 5.—The same as Figs. 3 and 4. Exposure with a soft tube.

A soft tube shows the outlines of the operator's wrist black. Tubes of this kind produce excellent skiagraphs of the bones of the hand and forearm, but are not powerful enough to represent structures.

Fig. 5 shows the bony outlines of the case, illustrated in Figs. 4 and 5, well. The backward dislocation produced by the tuberculous destruction of the ligaments can be recognized, but the tuberculous destruction is not marked.

FLUOROSCOPY (ROENTGENOSCOPY).

If the rays fall upon a screen covered with fluorescing salts, such as tungstate of calcium, platinocyanide of potassium, or platinocyanide of barium, fluorescence is caused on it. The human hand, for instance, if placed between the tube and a screen evenly covered with one of the flourescing salts, shows the condition of its bones distinctly. Even the soft tissues can be distinguished to some extent. Up to the present day the platinocyanide of barium, as it was first used by Roentgen, has proved to be the best fluorescing material.

The use of the fluorescing screen is facilitated by attaching it to a

suitable framework, formed like that of a stereoscope, the body of which is of a tapering form. The large end of such an instrument, generally called *fluoroscope*, should contain a piece of cardboard, on the inner surface of which the fluorescent salt is distributed, while the small end of the apparatus has two apertures, formed in such a manner as to fit over the eyes of the operator.

For examination with the fluoroscope a room must be chosen, which can be darkened at will.

A rough sketch may be obtained from the screen by simple tracing (Fig. 6).

Hard tubes should not be employed for fluoroscopic work on account of their great penetrating power which permits of but little contrast. A tube of medium hardness gives the best fluoroscopic differentiation.

FIG. 6.—Apparatus for Tracing.

SKIAGRAPHY (ROENTGENOGRAPHY).

As previously stated, the structural details can be shown exactly on the photographic plate, and it is the skiagraph only which permits of the thorough study of the various features of a lesion. Its comparison with the normal skeleton will make the abnormalities evident at once and will help the physician to a thorough judgment of the case; and the value of a skiagraph for future information—especially in case of complicated fracture for forensic purposes—should not be underestimated. Therefore whenever exactness of result is desired, fixation on a photographic plate is to be preferred. The photographic technique can easily be learned.

The development of a skiagraphic plate is practically the same as that of an ordinary photographic plate exposed to sunlight. There is no doubt that the anatomical knowledge of a physician makes him more fit to develop the important parts of a plate properly. It is, besides, a great advantage if the physician is able to develop the plates himself, since he learns the result at once, while the sending of a plate to a photographer involves a great loss of time.

The most important requirement for photographic work is a well-sensitized plate. As is generally known, plates of this kind are made by covering them with a hard, white, sensitized gelatin film. Those made especially for skiagraphic purposes are extremely sensitive; therefore they must be well guarded against injury by too strong a light while developing, or by traces of diffused light entering the dark room or the envelope, lens, or camera. As the object to be skiagraphed must rest on the film side, it is important to ascertain before the exposure which is the film side. In holding the film against the red lantern light, its dull appearance becomes evident, while the plain glass side shines. But as will be seen below, the light should not be trusted too much; consequently the test had better be made by the touch. A practised finger will ascertain at once which the sensitized side is. In case of doubt, however, the moistened finger may touch the corner of the plate which, if covered by the film, will feel sticky.

The developing of the plate must be done in a dark room. Ruby light is recommended as the best "dark-room light." It is used while the plates are taken from their boxes and put into a photographic envelope or into a plate holder. The latter must be provided with a non-metallic sliding cover.

Some manufacturers furnish specially prepared plates which are separately wrapped and sealed in black and in yellow envelopes. But while it is very convenient to have the "individually wrapped plates" ready for immediate use, it must be remembered that the wrappers affect the sensitized surface and consequently injure their keeping qualities. They are therefore not to be recommended.

If several exposures of the same object must be taken, as, for instance, in cholelithiasis, a box of the shape of a drawer must be put underneath, the plates being inserted through the open side space without dislodging the object.

Developing is also best begun in the dark; a Carbutt's ruby light lantern may conveniently be used later on, since ruby color, being the least actinic, offers the best protection.

Among the various *developers* recommended may be mentioned hydrochinon, hydrochinon-eikonogen, and metol-hydropowder. The latter seems to be especially fit for short exposures. Very large plates should be immersed in water before the developer is used.

The strength of the developer, which is to be mixed with cold water, should be moderate. During the hot weather the developer must be more diluted and cold, while it may be stronger and warmer (70° F.) during the cold season. Too warm and too strongly alkaline developers cause stains and fog on the plate. After the mixture is properly prepared it is poured into a hard-rubber tray and the plate

is placed in it. If the plate is rocked from side to side now, say for about three minutes, the image appears.

The plate now remains in the solution for another two minutes until it appears dark and the image has nearly entirely disappeared. If there is lack of clearness, a few drops of a ten-per-cent. solution of bromide of potassium should be added.

If there should have been over-exposure, the plate must be thoroughly washed and may then be finished with bromo-hydrochinon developer. But if undertimed, the details not being distinct, a fresh developer must be used. Then the plate is immersed in a tray containing water to which some sulphite and carbonate of sodium has been added, and is left in this solution until the details come out more clearly. The same procedure may be repeated if the image does not appear to be satisfactory.

If the condition of the development harmonizes with that of the exposure, no correcting steps are necessary, and the plate is simply taken out of the tray. The plate is now washed in pure water and then placed in a second tray for the purpose of fixing the image. This second hard-rubber tray contains a solution of hyposulphite of sodium.

After the plate has remained in this solution for about four minutes, its light color will change into black. Now the image is regarded as fixed, and the plate may be exposed to light without being injured. The process is completed by washing the plate in running water for thirty minutes and then setting it upon a stand.

If the plate is insufficiently developed it may be strengthened with a so-called intensifying solution. This process might be easily overdone. In such an event correction may be effected again by a "reducing solution."

Albers Schoenberg has recently recommended the so-called "stand-developing" with glycon as the best method for skiagraphic work. The plate is immersed in the glycon developer for from fifteen to sixty minutes, being inspected every ten minutes, until it appears satisfactory. Then it is well washed, and kept in the fixation tray for fifteen minutes.

Foggy negatives may sometimes be caused by a decomposed developer, or by one containing too much carbonate of sodium or potassium without bromide. Weak negatives with clear shadows indicate under-development. Too strong negatives with clear shadows indicate under-exposure, while weak negatives with distinct details in the shadows are produced either by over-exposure or by too weak a developer.

Method of Roentgen Examination.

The advantages of fluoroscopic examination are especially marked when organs are studied while they are in motion. The excursions of the diaphragm, the pulsation of the heart, the pericardium, the relations of the thoracic viscera, the joints, the larynx, and the zygoma can be observed while functioning. The disadvantage of fluoroscopic examination consists in the production of the numerous fluorescing impressions which, by succeeding each other with great rapidity, are apt to deceive the human eye, wherever the features of the lesion are not distinctly marked. Fixation of the condition to be examined on a photographic plate (skiagraphy) is therefore to be preferred as a rule.

Fluoroscopic examination is of great value as a preliminary procedure in fractures and dislocations, since it calls attention to the seat of the injury. It furthermore determines the best position of the limb for proper fixation during skiagraphic exposure, so for instance that angle of flexion or extension in which the injured portion can be brought out best on the plate.

The region to be examined must be freed from clothing. It is true that a good tube permits of irradiating, even through an overcoat, but small details become lost. So the shadow of a button or a buckle may just cover a region of special importance. Fluoroscoping may be done while the patient stands before the examiner who is seated in a chair. The head is fluoroscoped best while the patient is seated in a chair. In fluoroscopy of the lower extremities the patient may be seated in a chair placed on a table, so that the soles of his feet rest on the latter.

As a rule tubes of medium hardness are most useful in fluoroscopy.

In order to study any region of the body with leisure and to observe its structural details, a skiagraphic* exposure is necessary. In most instances the patient is skiagraphed best in the recumbent position. This may be done on one of the tables, which are provided with a box for receiving the photographic plate. The patient may as well be placed on the carpeted floor. This simple arrangement offers the advantage of a wide operating field around the patient. The extremities can be placed in any position desired, and blocks, sand-bags, large books, etc., may be used to surround and immobilize the area to be skiagraphed. In the case of nervous children there is no fear of their falling from the table. Excitable patients are also more easily per-

* This opportunity may be taken to object to the much-favored expression "radiography," which, as many other modern terms constructed by violent word-composers, is a hybrid.

shaded to place themselves on the floor than on the table. In some cases a table with a movable stand is convenient (Fig. 7).

Thick portions of the body reflect the rays diffusely. So, for instance, in making an exposure of the pelvis of a fat individual each muscular portion irradiates the whole plate individually, so that the contrast is considerably diminished. To obviate this lead diaphragms have been constructed, the opening of which does not permit a larger amount of light to pass than the reproduction of the area to be traversed requires. Thus the injurious rays are kept off, the effective cone of light only being projected on the plate.

The *position* of the patient during irradiation is of importance. The nearer the area to be irradiated is to the tube, the clearer and

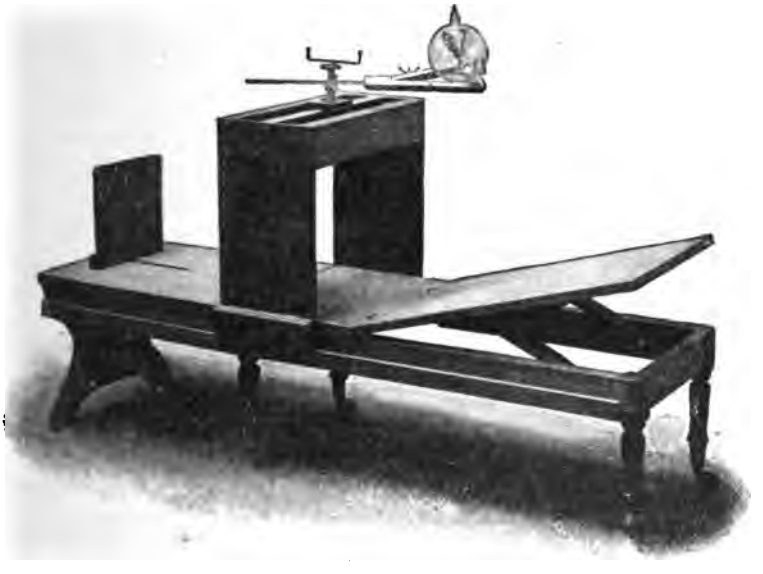


FIG. 7.—Roentgen Table with Movable Stand.

more promptly appears the image. The fact must not be lost sight of, however, that the nearer the tube is the greater is the danger of burning the patient, but this, as will be seen later, need be considered in repeated exposures only.

The position of the special part to be skiagraphed is also of great importance. It is difficult to lay down any definite rules for this, since each case demands a special perspective. In general, however, the following directions may be adhered to:

The forearm is best seen in supination, although this position is by no means the most comfortable for the patient. The upper arm and the thigh can be taken in any position. The hand is usually traversed from the dorsum to the palm. The humero-ulnar joint

should be taken transversely, while the humero-radial joint had better be irradiated from the flexor to the extensor side.

The foot, from the toes up to the upper third of the metatarsus, is best skiagraphed in the direction of the dorsum toward the planta pedis. Farther back the first and third cuneiform bones and the scaphoid present an obstacle, so that it is advisable to irradiate these portions of the foot transversely by having its outer surface resting on the plate. By this procedure the isolated shadows of the astragalus, the calcaneum, the cuboid, the scaphoid, and the fourth and the fifth metatarsal bones can be represented.

The knee-joint is reproduced best by resting the external condyle on the plate. The leg should be skiagraphed while its external surface is placed on the skiagraphic plate, the knee being bent and the thigh rotated outward. The hip-joint is preferably taken by turning the patient from his recumbent position inwardly so that the anterior axis of the thigh forms an angle of from thirty to forty degrees with the underlying plate. The opposite hip is elevated and supported accordingly.

Absolute rest is the *conditio sine qua non* for a successful exposure. The patient must rest as comfortably as possible. The trunk must be supported by heavy pillows and the extremities by sand-bags. Intelligent mothers generally succeed in lulling their babies into sleep. By manipulating the apparatus with a low current first and then increasing it gradually, its monotonous noise sometimes acts as a lullaby. Anæsthesia for the purpose of keeping patients quiet should be resorted to only under the most pressing necessity.

The density of the objects to be skiagraphed is of course a determining factor for the distinctness of the skiagraph. It is well known that the higher the atomic weight of any element is, the more energetic the absorption of the rays will be. The inorganic substances of the body therefore, such as the salts of lime in the bones, absorb more light than the surrounding soft tissues; consequently they are but slightly permeable by the rays. The more lime salts the bone contains, the less permeability exists and the more distinct the silhouette will be on the photographic plate. Thus compact bone tissue shows a very much more distinct image than do the medullary or spongy parts. The special structures of the different bones can be recognized so well, in fact, that the finest details of the structure of osseous tissue can be represented. This offers a splendid opportunity for studying the transformation of bone tissue, which was formerly a sealed book.

The organic tissues of the human body show permeability of a medium degree. The degree of translucency of the muscular layer of the heart or of a hand or foot corresponds with that of a liver or kidney of the same thickness. The tissues of the nerves and blood-vessels

are somewhat less permeable. This similarity of the degree of transparency explains why in skiagraphs of the soft parts no special variety of tissue, such as muscles, tendons, ligaments, nerves, or vessels is individually marked. With very soft tubes and by carefully developing the skiagraphic plates, however, hyaline cartilage can be distinctly and tendons and ligaments faintly differentiated. The greater distinctness of some portions is therefore not due to the character of the individual tissue, but to the greater thickness of the irradiated mass.

Since cartilage is permeated by the rays as a rule, normal joints appear enlarged. The epiphyseal lines are well marked. In children the line of ossification appears translucent, and this has often given rise to false interpretation, especially to an incorrect diagnosis of fracture. The infantile vertebræ appear widely separated from each other, thus giving the erroneous impression that there is a pathological hiatus.

The area to be skiagraphed must be brought as near the plate as possible. Exposures for special purposes require special appliances. In skiagraphing gall-stones, for instance, pillows must be placed underneath the clavicles. Thus an elevation is produced permitting of the protrusion of the gall-bladder, which is then brought nearer to the plate. The approximation is increased by turning the body slightly to the right and raising and supporting the left side accordingly.

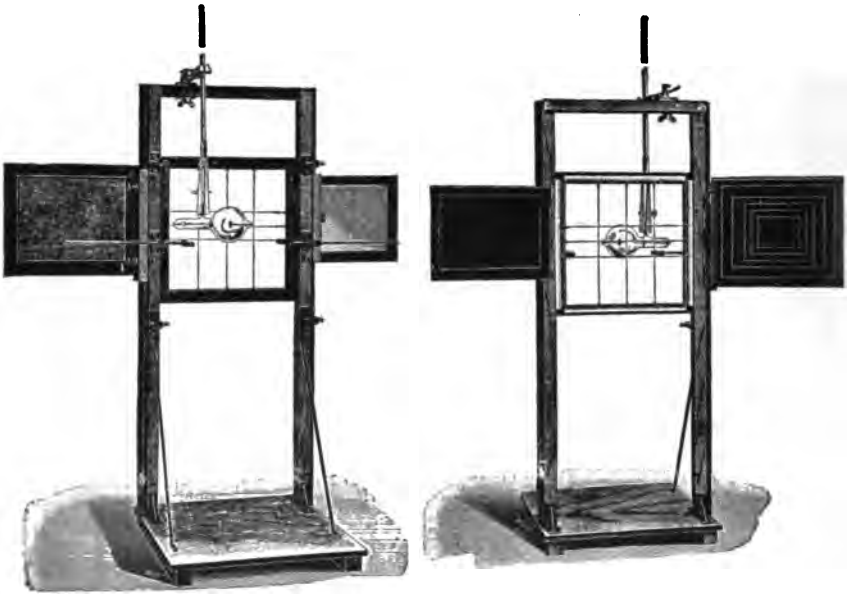
As the patient has to assume the abdominal position, a landmark indicating the position of the gall-bladder must be made either with nitrate of silver or with a special skiagraphic pencil on the dorsum in order to secure the proper focus. In this way it will be possible to direct the rays vertically on the marked area.

Another point of importance is that the rays should traverse the abdomen in a slightly lateral direction so that the dense tissue of the liver is not permeated in its whole diameter. The focus line may, in other words, form an angle of about seventy degrees with the dorsum. Thus some of the rays reach the calculi before they are absorbed by the compact liver tissue. The disadvantage of oblique irradiation is that biliary calculi appear somewhat larger than their natural size. When a protrusion, palpable in the region of the gall-bladder, indicates an enlarged gall-bladder, direct irradiation should be attempted, the shadow of the liver not obscuring it then. In such cases, however, the diagnosis of cholelithiasis can be made without skiagraphic examination.

In skiagraphing *foreign bodies* it must also be remembered that their size varies with their distance from the tube. In the case of oblong bodies great errors as to their exact size may be made, if a second exposure in a different projection plane is omitted. Early in the Roentgen era the author was not little surprised in the case of a seamstress in whose palm a needle fragment had entered in a perpen-

dicular direction. The plate, while indicating the presence of the needle distinctly, created the impression that the fragment was only 2 mm. long. When extracted, its length was found to be more than an inch. The rays had reached the hand in a perpendicular direction so that the circumference of the fragment was reproduced rather than its length. A side view, of course, would have cleared up the error at once. In fractures also exposures in different projection planes are almost a necessity.

For locating the position of foreign bodies various ingenious but somewhat complicated forms of apparatus have been devised. The



A *B*

FIG. 8.—Hoffmann's Stand for Measuring. *A*, front view; *B*, back view.

wire letters used by the author for registration may also serve as landmarks in a simple manner by being attached by means of adhesive plaster to the region of the body to be irradiated, after it has first been marked with the skiagraphic pencil. Wire letters may also be placed on the plate just below a wound or a scar, indicating the entrance of a foreign body. If there is a wound sinus a probe may be introduced as far as it is possible. Thus the extent of abscess cavities may be ascertained. (See the section on foreign bodies in the lungs.)

The main principle of the apparatus devised by Hoffmann consists in the construction of registering wire screens (Fig. 8) which can be moved in various directions. Apparatus of this kind, however, permits only of measuring the shadow of the foreign body, while its nat-

ural size must be guessed at. Donath's modification, which allows the movement of the tube above a millimetre scale, the tube being placed perpendicularly at a measured distance, gives very nearly the exact size of the foreign body.

For locating foreign bodies in the skull the wire letters recommended above may also be used by being fastened to a wire headband wound around the temples. Then the intervals between the individual letters must be measured. The same procedure can be carried out on the extremities by winding the wires around the limb and also fixing them at the plate. The same principle can be utilized on other regions of the body.

The tube-holder is placed best between the Ruhmkorff coil and the patient. The wires connecting the secondary terminals of the Ruhmkorff coil with the tube may be loosely hooked in the terminals. These must be kept separate from one another in order to avoid shocks. Their calibre should be very small, but they must be surrounded by a thick layer of insulating material.

The anticathode should be connected with the anode, and the anode with the positive electrode of the Ruhmkorff apparatus, while the cathode is to be connected with the negative electrode of the apparatus. The tube-holder must permit the tube being moved in any position desired. A false direction of the current is indicated by the appearance of a marked shadow originating from the anticathode and the formation of blue light.

The *distance* of the tube is also a matter of great importance. Various distances produce various relations. The smaller the distance is between the tube and the plate, the larger appears the silhouette of the irradiated part. The smaller the silhouette is, on the other hand, the more correct the proportions of the tissues appear.

Under ordinary circumstances the tube should be as near the object to be skiagraphed as possible (four inches), in order to make the exposure as short as possible. As an average it may be assumed that an equally good skiagraph of the human hand is made when the distance is four inches, the exposure lasting half a minute, as when the distance amounts to eight inches, the exposure lasting a whole minute.

If a good tube is used in connection with a Wehnelt interrupter it may be expected that less than a half a minute exposure suffices for the reproduction of the structure of an adult's hand. The forearm requires a little over a minute, and the elbow, the arm, and the foot two to two and a half minutes. The leg, the knee, and the thorax take from three to four, the skull five to six, and the pelvis from five to eight minutes.

The question of the length of the exposure, however, is a delicate one and up to the present time is still *sub judice*. It is impossible to

lay down absolute rules, and experience and instinct must to a great extent guide the examiner. A failure often shows how it should be done better the second time.

Examination of Special Regions.

Head and Face.—The facial portion of the skull can be clearly outlined, but the larger portion of the cranium is darkened by the shadow of the opposite cranial wall. To study the relations properly, a sagittal and a frontal exposure must be made. If the left side of the head rests on the plate, the irradiation taking place from the right, the soft tissues and the galea aponeurotica are recognized as a light shade. The soft tissues of the nose, lips, and the chin are very conspicuous.

Of the bony parts the external occipital protuberance, the orbital, nasal, and sphenoid bones, and the light shadow of the external auditory canal are seen. Below the latter, the small cavities of the mastoid process may be perceived; the zygoma is also quite distinct. The nasal bones and the superior maxilla, showing the quadrangular shade of the antrum of Highmore, can be especially well represented.

The nasal process, the hard palate, the alveolar process and its cells and teeth, and the inferior maxilla, showing its mental foramen, the protuberance, the external oblique line, the angle with its two processes, can be well demonstrated. With these osseous structures, the shadows of the tongue and the velum palati contrast well. The motions of the velum palati and of the tongue can be easily studied. Schneier has considerably increased our knowledge on the physiology of phonation by his fluoroscopic studies.

By placing the patient's face on the plate and a tube behind it, the margins of the orbit, the frontal and nasal cavities, and the nasal bones appear well outlined.

In infants the details can be much better represented. Even the interior of the ear (cochlea and semicircular canals) can be shown.

Fig. 9 represents a boy, five weeks of age, who had a spherical, non-pulsating tumor, of the size of an orange, projecting from the naso-frontal region, and sinking downward to the alæ nasi. At birth the tumor was a trifle smaller. The walls of the tumor were thin, and the integument appeared normal. Contractions of the tumor were observed, especially while the child was crying. During sleep the tumor appeared somewhat smaller. There was exquisite fluctuation, and the contents could be pressed almost entirely within the skull, this causing no reaction. Pulsation of the brain could not be detected, nor could the border of the cranial opening be felt distinctly. In view of these facts, especially of the inability to palpate a solid mass with certainty, a meningocele was suggested.

The Roentgen rays, however, modified the diagnosis. A skiagraph showed behind the light shadow, representing the fluid, a dark one, which had to be interpreted as that of a solid mass, confined to the area of the large triangular bony opening. That this was cerebral substance was verified by the subsequent operation. The skiagraph

FIG. 9.—Cephalomeningocele in an Infant of Five Weeks.

also showed that the nasal bone was shifted downward so that the interspace of the width of a man's thumb was left between it and the frontal bone.

To *locate foreign bodies* in the eyeball, the exposure is best made in the oblique direction, so that the foreign body appears either in front of, or behind, the orbital margin. In this way Dahlfeld and Pohrt succeeded in skiagraphing birdshot of the size of 0.4 to 1 mm. For localization of foreign bodies in the eyeball, it is advisable to place miniature letters at the inner and outer ends of the eyelid and one at the orbital margin. The localization of foreign bodies in the skull is sometimes connected with considerable difficulty. If foreign bodies are situated in the bones, two skiagraphs at least are required, one to be taken antero-posteriorly, and the other laterally. By simply crossing their diameters diagonally, the distance from the outer surface can be determined. The same principles of localization, more or less modified, apply to the intracranial localization of foreign bodies.

The Roentgen rays have furnished valuable contributions to our knowledge of rhinology. The frequent presence of foreign bodies in the nose gives many opportunities for their use. The examination of

the frontal sinus is of still greater importance. The absence of nasal bones and of the hard palate can be well studied. In suppuration of the antrum of Highmore the skiagraph enables us to detect the affected side, which shows a much darker shadow than the normal.

The relation of the dental roots and their position, the presence or the absence of the milk teeth, as well as of the permanent teeth, in children, or of an old root, or foreign bodies (fillings, pieces of chisel broken off, for instance, while excavating a carious tooth), and the extent of an alveolar abscess can be clearly demonstrated. (Compare Fig. 10, which shows transverse location of tooth in the mandible.)

Sometimes it is of great forensic importance to determine the age

FIG. 10.—Osteoma of the Mental Portion of the Inferior Maxilla, in a Girl of Thirteen Years.

of an infant corpse by skiagraphing the teeth. As a rule, it will suffice to place the face portion nearest the tooth in question on an ordinary Roentgen plate. If fine details are demanded, flexible films may be introduced into the oral cavity, where they will adapt themselves to the contours of the maxilla. In a case of severe neuralgia the question arose whether an old root was the cause of the evil. The skiagraph showed that the small screw of the adjacent artificial tooth had been inserted in the wrong direction. After it was unscrewed the pain ceased.

Neck.—The best exposures are made by turning the patient sidewise. In this position the cervical vertebræ are better shown, the angle of the inferior maxilla not overshadowing their upper portion.

The dark shadow of the hyoid bone, as well as the lighter shadow of the larynx, the epiglottis, and the trachea are well represented. The œsophagus, while not conspicuous, can be made out behind the trachea as a hollow space. The vertebral bodies, the spinous and transverse processes, as well as the intervertebral foramina, appear very clearly.

Aneurysm of the carotid or the subclavian arteries is demonstrable. Tumors of the larynx, especially chondroma, and ossification of the cartilages are easily recognized. Exploratory incision for suspected foreign bodies in the pharynx, tonsils, larynx, trachea, and œsophagus has become unnecessary. The rays, as explorers, have indeed realized

FIG. 11.—Tuberculous Glands of the Neck.

the old ideal desideratum: *cito, tuto, et jucunde.* Whoever has felt the uncertainty in diagnosticating foreign bodies in these regions, and especially who has been tempted to resort to adventurous procedures, must keenly feel the blessings that the rays have brought. If the Roentgen rays had done nothing else but located foreign bodies in the throat, they would remain one of the greatest blessings to suffering humanity.

The various types of goitre may also be studied. Wherever calcification is found, thyroidectomy should be advised, provided the disturbances are of a severe character. Otherwise internal treatment combined with the local injection of iodoform ether is to be tried.

Tuberculous glands can also be shown if there are thick, cheesy, calcareous deposits. Fig. 11 is impolite enough to demonstrate the presence of thirty-two little glands, left behind by the author after he thought he had performed a "radical" extirpation of the cervical glands one week previously. This shows that it will be impossible to remove all tuberculous glands at one operation.

FIG. 12.—Hypertrophy of the Left Ventricle after Acute Rheumatism, in a Girl of Thirteen years.

Chest. — The dorsal vertebræ, the ribs, the clavicle, and their injuries and diseases, and those of the heart, lungs, pleura, and diaphragm can be easily seen. Foreign bodies in the thoracic cavity are clearly shown, and most diseases of the thoracic cavity can be studied by means of the Roentgen rays. An enlargement or displacement of the heart, and effusion in the pericardium can be shown, as well as aneurysm and the various kinds of mediastinal tumors.

Pneumonic solidifications, phthisical foci, cavities, abscesses, tumors, bronchiectasis, emphysema, and retraction of the lungs can be recognized by fluoroscopy as well as by skiagraphy. Effusions in the pleural cavity and also fibrous degeneration of the pleura are noted. Irregularity of the excursions of the diaphragm can be well studied. Nowhere does the usefulness of the fluoroscope become so apparent as it does in chest work, because the intrathoracic organs can be observed while in motion.

In skiagraphing the patient in the dorsal position (anterior irradiation), the spinal column as well as the posterior portions of the ribs with their heads, necks, and tubercles become apparent, especially at

the right side (Fig. 12). The direction of the posterior ribs is downward, while that of the anterior is upward. The image of the anterior aspect of the ribs is naturally diffused on account of the much greater distance from the plate.

In skiagraphing anteriorly (posterior irradiation), the patient lying on his abdomen, the clavicle, the sternum, and the adjoining ribs are well defined. The spinal column and the posterior ribs appear diffused. The heart being situated so near the anterior chest wall, presents its outline well marked. The shadow of the large blood-vessels is less distinct. The shadows of the normal bronchi, especially the middle portions, are very light. The left middle portion of the lungs must be studied from the side, because if examined from the front it becomes obscure by reason of the large triangular shape of the heart.

The treatment of scoliosis, kyphosis, and lordosis can be well controlled by repeated skiagraphic observations.

FIG. 13.—Cancer of the Œsophagus, Beginning at the End of the Wire Sound, in a Man of Fifty Years. A bronchial gland can be seen in the fifth intercostal space.

Inflammatory processes, like spondylitis, can be differentiated from fracture of the spinal column. Tuberculous foci in the vertebræ are also demonstrable. The same is true of osteomyelitis and necrosis.

In the case of a tumor of the chest wall (fibroma, osteoma, chondroma, osteochondroma, osteosarcoma, etc.), the question as to how far the pleura and lungs are involved is of great importance and may determine whether removal still offers any hope of benefit for the patient. The same may apply to advanced carcinoma mammæ, cases of which, thanks to the wonderful advances of surgical science, are rarely seen at the present time.

The outlines of the heart are better seen during fluoroscopy than

in skiagraphy, its regular contractions producing a diffuse shadow on the plate.

In fluoroscoping, the regular expansion of the thoracic walls during each inspiration can be studied, the ribs diverging from each other and the diaphragm descending. The movements of the heart can be distinctly seen. The observations of Williams and Benedikt demonstrated some physiological errors in regard to the mode of contraction of the heart, and cleared up some obscure points. That the heart does not empty itself completely at each systole becomes evident by the presence of a large blood shadow. Thus we learn that the contractions of the heart are not of the extent assumed heretofore. In proportion to the amount of blood filling the ventricles, the shadow of the apex appears lighter or darker.

During deep inspiration it can be observed that the diaphragm becomes separated from the heart, which proves that the heart is suspended by its blood-vessels and is not supported by the diaphragm.

The importance of ascertaining the exact size of the heart should also not be under-estimated. For examination in this direction, at least two skiagraphs, under different projection planes, should be made in order to avoid errors. The principles of localization should be well observed.

To localize stenosis of the œsophagus, a rubber tube containing thin, flexible steel wire in spiral form, may be used, the skiagraph demonstrating where the stoppage of the tube occurs.

In the case of carcinoma œsophagi, illustrated in Fig. 13, the sound stops on a level with the upper margin of the fourth dorsal vertebra. The skiagraph indicates the extent of the tumor as well as the infiltration of a bronchial gland, which explained the respiratory disturbances of the patient.

For fluoroscopic examination, it is advisable to administer an opaque substance, like subnitrate of bismuth, in a wafer. The tube is adjusted in front of the patient's right shoulder in such a manner that the chest is irradiated from the right upper anterior aspect toward the left lower posterior. The bismuth (about gr. xv.) can be seen during the act of swallowing as a marked shadow that becomes diffused after a few seconds; then a portion of it is detected in the stenosis, while the other parts of the œsophagus show nothing abnormal.

Aortic aneurysm can also be advantageously studied. In the case of an Italian laborer, a pulsating tumor was detected at the left intraclavicular fossa. A diagnosis of aneurysm of the subclavian artery had been made and ligation advised. In the mean while, several skiagraphs were taken that showed the presence of aortic aneurysm, the supraclavicular tumor being merely a portion of it. Iodide of potassium was administered and the supraclavicular tumor disappeared

entirely. The size of the aneurysm had considerably decreased, as was shown by the skiagraph (Fig. 14). In harmony with the anatomical diagnosis is the excellent condition of the patient, who has been under observation for two years.

It should be borne in mind that under normal circumstances the aorta is seen in the left mediastinum at the first intercostal space. A sac-like bulging of the arch, showing considerable pulsation above

FIG. 14.—Aneurysm of the Aorta, Considerably Reduced in Size by Treatment.

this space, points to the presence of aneurysm. Vehement pulsation, if there is no sac-like bulging, points to aortic insufficiency.

In a most extraordinary case of aortic aneurysm, it was possible to demonstrate not only complete atrophy of the sternum down to the xiphoid process, and of the sternal portions of the clavicle, but also the extension of the heart beyond the parasternal line and the downward displacement of its apex. The oval shape of the heart was dis-

tinctly seen, and was easily distinguished from the aneurysm, the enormous intrathoracic extent of which was plainly shown. Another skiagraph of the same case showed the aortic arch. The patient succumbed to pneumonia six months after the skiagraph was taken, and the diagnosis was verified by the autopsy.

If we realize that the rays enable us now to recognize aneurysms in their earliest stages, it becomes evident that frequently prophylactic measures can be used that may counteract any further growth of the aneurysm. By means of fluoroscopy then it can be ascertained whether improvement, arrest, or still further expansion is taking place under treatment. See Fig. 14.

The diagnosis of arteriosclerosis, while very easy on the surface of the body, has hitherto been very difficult in the deeper tissues. According to the text-books on internal medicine, the thickening of the intima cannot be recognized if it is confined to a small area. It hardly need be emphasized how important it is to know whether in a given case of sclerosis of the radial artery there exist foci in other vessels. Nor can it be a matter of indifference what may be the number of these obstructive foci, and whether a large artery, such as the aorta, or only a small one, such as the temporal is concerned. The presence of a large number of foci means a loss of propelling energy in the circulation, which can be compensated only by the increased working power of the left ventricle. The arterial pressure thus becoming higher, hypertrophy of the overworked ventricle will be the most natural consequence. If such foci are recognized at an early stage, proper prophylaxis can accomplish a great deal in preventing secondary disturbances. The prognostic significance of an exact knowledge of the condition of the arteries is also evident. The Roentgen rays give us a more reliable method of ascertaining the condition of the vessels, and this in nearly every part of the body. So-called intermittent limping is thus sometimes explained by the early recognition of sclerosis of the arteries of the foot.

In a case of sclerosis of both radial arteries the forearm, head, neck, femoral and aortic regions were studied skiagraphically. Nowhere did the plates show indications of degeneration of any artery except in the forearm. From the negative state of the other skiagraphs the conclusion was drawn that the patient's arteriosclerosis was confined to the radial and the anterior interosseous arteries—a limitation that harmonized with the good general condition and absence of palpitation, dyspnœa, and vertigo.

The arteries can be well seen in the cadaver, after they have been injected with a material not permeable by the rays, as, for instance, a mixture of calcium sulphate or of 33⅓-per-cent. blue ointment. In this way a representation of the smallest arterial branches can be ob-

tained, and images of the arterial branches of the lungs, kidneys, spleen, and the brain can be beautifully represented by a stereopticon.

As to the type and size of mediastinal tumors, much more reliable information can be obtained by combined fluoroscopy and skiagraphy than by percussion and auscultation. The examination must be made in different positions. While aneurysms, as stated above, are usually characterized by the presence of pulsation, and mediastinal tumors by the absence of pulsation, it should not be forgotten that mediastinal tumors may also appear pulsating, the pulsation being communicated. On the other hand, there are aneurysms that do not pulsate.

Pericarditis is not infrequently observed after a fracture of the ribs, if a splinter has pierced the pericardium. The true character of the trauma can be elicited by the Roentgen rays. If, for instance, the clinical symptoms are slight, and the rays show no displaced splinters in the direction of the pericardium, medical treatment alone is in order. Even if a bullet, after having fractured a rib, has entered the pericardium, there may be no need of surgical interference if no severe symptoms are present.

The evidence of a large bone splinter pointing toward the pericardium is an urgent indication for exposing the pericardial sac after the resection of the left fourth, fifth, and sixth ribs. These need not be resected in their totality, but may be folded up at their sternal junctions like a bone flap of the skull. The diagnosis of pericardial adhesions may also be verified by fluoroscopy, which shows limited expansion.

In regard to the study of the diseases of the lungs and pleura it may be maintained that whoever does not master the principles of auscultation and percussion is not fit to comprehend the fluoroscopic or skiagraphic signs. There are conditions in these organs that can be better elicited by the so-called physical methods and others that can be ascertained only by means of the Roentgen rays. While the rays show small tumors or infiltrated foci that, on account of their central location, cannot be diagnosed by the old physical methods, they have the disadvantage always of showing the thoracic image *in toto*, that is, they represent all the shadows of the tissue situated before and behind the diseased area at the same time.

At the early stage of tuberculosis of the lungs, valuable information can be derived from irradiation. Skiagraphy is of greater value in this connection than the study with the screen. Solidification and atelectasis as well as exudation and calcification can be well demonstrated. The true nature of the various shadows is often better understood if, after skiagraphic representation (see Fig. 15), the thorax is also fluoroscoped in different positions.

Thus interlobular exudation may be differentiated. The localiza-

tion of lung abscess, of echinococcus, and gangrene of the lungs, etc., is simplified by examining in different positions. Abscesses and gangrene of the lungs appear as light circumscribed foci that contrast with the darker shadows of their walls (Fig. 16).

Pleuritic effusions show a marked opacity through the fluoroscope. The larger the amount of effusion the greater the degree of opacity. In pyothorax the opacity is somewhat less complete than in hydrothorax.

Especially on the right side the outlines of the liver show a marked contrast to the lower boundary line of the effusion. The inner boundary line of the effusion generally appears convex, but if the patient

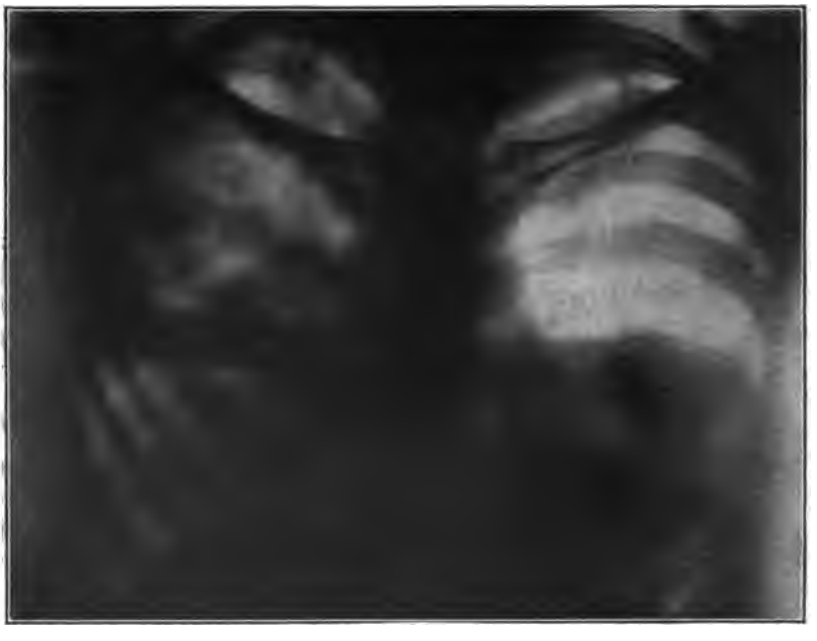


FIG. 15.—Tuberculous Foci in the Right Lung of a Woman of Thirty-five Years; an advanced stage of pulmonary tuberculosis. (Long exposure.)

inspires deeply or if he coughs violently it loses its convexity and becomes horizontal. By changing the position of the patient, of course, displacements of the effusions are observed accordingly. Uniform transparency above the effusion points to the result of a simple inflammatory process, while constant opacities of an irregular appearance justify a suspicion of a beginning of tuberculosis.

As a rule it is found that the area of dulness corresponds to the area of shadow. It is natural that the representation of cavities in tuberculous lungs should not be attended with any technical difficulties. Mediastinal and pulmonary tumors may be recognized, over which no dull areas pointing to their presence were elicited by percussion.

Swollen bronchial glands have also been diagnosed by the rays. Hypertrophied pleuræ show a very distinct shadow according to the thickness of their tissues.

The extent of a pyothoracic cavity can be represented by filling it with iodoform glycerin. The subnitrate of bismuth, which is not permeable by the rays, furnishes a still more marked contrast; but as it interferes with the treatment, its use cannot be recommended for this especial purpose. The rays have also proved that after subperiosteal resection of a rib, the exsected portion is always more or less reformed (see Fig. 16).

FIG. 16.—Abscess of the Lung, Exposed after Rib Resection.

Hydropneumothorax shows the very dark outlines of the exudation in contrast to the light shadow of that intrathoracic area that contains air. The dark boundary line of the exudation can be recognized by the fluoroscope as an ascending and descending line during respiratory movements.

Localization of bullets in the thoracic cavity is not always easy. The temptation to extract bullets that cause no disturbance is greater than formerly, a fact that is not to be registered among the advantages of the Roentgen rays.

Nowhere is the necessity of careful interpretation of skiagraphs so apparent as in thoracic diseases. It is utterly impossible to instruct a non-medical skiagrapher and to impress upon him the necessity of emphasizing certain points. If the physician does this work himself, he will be able to judge much better. But even then a great deal of doubt as to the real nature of an abnormal shadow may exist. The

scientific physician must never be tempted to tax his power of imagination, but must base his diagnosis on all the methods at his command, of which the Roentgen rays, however, form an integral part.

Abdomen.—The study of the abdominal organs leaves much to be desired. The solid mass of the liver can be easily represented, but the intestinal loops are only occasionally well shown. The intestinal contents, especially those of the transverse colon, are recognizable. The outlines of the stomach can be made visible by substances impermeable by the rays. The spleen and kidneys are rarely demonstrated at the screen, but can be outlined by skiagraphy. Below the shadow of the liver, especially of its left lobe, the lower ribs are clearly seen. The triangular shadow of the psoas muscle, from the beginning at the twelfth dorsal vertebra, is always easily recognized.

The chief practical results in abdominal skiagraphy have so far been obtained in the representation of the injuries and diseases of the lumbar vertebræ, and of concretions and foreign bodies. Thus fractures, dislocations, inflammatory processes, and growths of the lumbar vertebræ can be diagnosed, as can also calculi of the kidneys, ureter, bladder, prostate, urethra, gall-bladder, and hepatic ducts.

The liver is best represented with the subject in the abdominal posture. In new-born children its shadow is especially well marked. The position, size, and shape may give valuable information in many obscure hepatic ailments.

The diagnosis of *subphrenic abscess* is simplified by fluoroscopy as well as by skiagraphy, the space between the diaphragm and the lower boundary lines of the abscess showing distinctly.

Total transposition of the viscera was well represented in a case pictured in the *Annals of Surgery*, May, 1899. Never before has cholecystotomy for cholelithiasis been performed on the left side, as it was in this remarkable instance. The greatest usefulness of the rays in hepatic diseases is, however, displayed in the recognition of cholelithiasis.

Gall-stones have not been skiagraphed until recently. It was the privilege of the author to show the first undisputed skiagraph of gall-stones in the living subject at a meeting of the New York County Medical Association, in October, 1899. Gocht, Oberst, Rumpf, Dumstrey, and Metzger, who are among the best-known experts in skiagraphy, declared until recently that biliary calculi could not be represented. The last named is even responsible for the bold assertion that "nowadays nobody will any longer maintain that gall-stones can be skiagraphed," as "all experiments in this direction have proved to be failures"; and that "it appears hopeless that such experiments will give any other result in the future." But *errare humanum est!*

After many trying disappointments the author succeeded for the

first time in skiagraphing cholelithiasis in a woman, seventy-two years of age. The first exposure was made with a powerful tube on a single plate, and lasted ten minutes. After it was found how long it took with this tube to represent the liver and the os ilii, a second plate was exposed, this time for six minutes only. This second skiagraph showed the denser tissues less clearly, while the calculi were much more distinct. An exposure lasting seven minutes, one eight minutes, and another nine minutes were also made, all showing that the longer the time of exposure, the clearer the denser tissues and the more obscure the calculi appeared. It thus became evident that one exposure was not sufficient to determine the length of time required by each individual tube for the representation of each individual gall-stone type. This suggested that a test should be made first by making a short and a long exposure in a case of suspected cholelithiasis; that is, an exposure of about four minutes and one of six or seven minutes. By comparing the results, the proper time of exposure for the individual case can be estimated. For better identification, the contours of the organs, especially the liver, should be outlined by thin wire attached to the plate before the final skiagraph is taken.

The results, of course, are to a great extent dependent on the chemical composition of the biliary calculi, which is far more complex than that of urinary concretions. All the different types of calculi can be skiagraphed on a photographic plate. In this way we obtain a visual comparison of their permeability. The same calculi can then be irradiated through the living body, thus practically demonstrating the difference in translucence. The common biliary calculi, the most frequent type, are found to be quite permeable to the rays and therefore produce only a light shadow. If present in large numbers, the shadow is somewhat more conspicuous. Calculi composed of pure cholesterin are less permeable than those of the common type, and show a slightly more distinct shadow.

The stratified cholesterin calculi, on account of their admixture with calcium, show much less permeability, and therefore produce a distinct skiagraph. The mixed bilirubin calculi, which besides bilirubin-calcium contain traces of copper and iron, are less permeable than all the former varieties and consequently give a very distinct shadow. The same applies to the pure bilirubin-calcium calculi.

Calculi composed of pure cholesterin, on account of their mixture of calcium, show less permeability by the rays. In consequence, their outlines can be nearly as distinctly shown as those of the bilirubin-calcium calculi. But with an excellent tube, even the more translucent calculi can be represented. Recently, calculi that were only the size of a pinhead have been shown in the gall-bladder. Calculi of the hepatic ducts have also been represented.

These results, which could formerly hardly have been hoped for, are attributed mainly to the excellent quality of the tubes used, and their careful selection. These must be carefully studied, individualized, so to speak, just as different patients are to be judged differently although suffering from the same disease. The most important requisite for skiagraphic success in such delicate work is a strongly built and powerful tube, one that will bear a fifteen-inch spark for about five minutes without becoming too hot. Another important requirement of such tubes is that they should be of medium hardness, so that the rays will permeate the soft tissues without penetrating the dense tissues. A tube useful for that purpose can best be tested by the operator's own hand.

It has been found that the tubes used for the reproduction of biliary calculi display their best energy so long as they are comparatively new. Later on they show less contrast, just like very hard tubes, even if provided with an attachment for regeneration. If the tube works well from the beginning, the average time of exposure should be about five minutes in thin individuals, and about seven in stout ones.

The position of the patient while being skiagraphed is also an important factor. He should lie on his abdomen with about three pillows underneath his clavicles, as the elevation produced permits the protrusion of the gall-bladder, thus bringing the calculi nearer the photographic plate. The approximation is increased by turning the body slightly to the right and raising the left side.

Another point of importance is that the rays should not penetrate the abdomen in a vertical direction, but from the side, so that the thick and less transparent tissue of the liver is not permeated in its whole diameter. The direction of the rays should be such that they form an angle of about seventy degrees with the plate. The nearer the tube is to the plate the more distinct will be the picture. As only a small area shows distinctly on the plate, great care should be taken to place the tube in the proper place. A pencil mark should be made on the back to correspond to the site of the gall-bladder in front.

The disadvantage of oblique irradiation is that the calculi appear nearly twice as large as their normal size. When a protrusion palpable in the region of the gall-bladder indicates that it projects from the liver, direct irradiation is to be preferred. In order to exclude any possible source of error from intestinal contents the bowels must be thoroughly evacuated before irradiation.

By using this method, not only can the size, shape, and diameter of the gall-stones be determined in suitable cases, but they can also be localized. The importance of knowing whether there are also calculi in the liver besides those present in the gall-bladder needs no discussion.

The presence of calculi in the liver tissue explains why cholelithiasis

is often only partially cured by cholecystotomy. This fact shows why calculi have sometimes surprised the surgeon, who has thoroughly evacuated the gall-bladder, by their appearance a few days after the cholecystotomy. That in cholelithiasis sometimes hundreds of calculi are contained in the hepatic ducts is a well-known fact, but why calculi appeared after cholecystotomy has heretofore been explained only on the autopsy table.

It is evident that a positive skiagraph renders exploratory laparotomy for suspected cholelithiasis unnecessary. It can be ascertained by subsequent exposures whether any calculi have been dislodged or whether some have escaped. If they are of very large size, their removal by other than a surgical means would, of course, not be expected. So the question of whether or not operation is advisable in cholelithiasis may be settled by the Roentgen rays. When only small stones are present, there is a chance for medical treatment. When stones are found too large to pass the common duct, medical treatment can only be palliative, and cholecystotomy should be performed as soon as the calculi prove to be a source of irritation.

It is appreciated that the method given for diagnosing biliary calculi is incomplete and needs further modification and improvement, as there are many delicate technical details on the correct appreciation of which success depends. Skiagraphy of biliary calculi is not so perfect a diagnostic method as that of renal, ureteral, and vesical calculi. While a negative result in the case of suspected urinary calculi can now pretty safely be taken as the evidence of the absence of calculi, the same cannot yet be said of biliary calculi. But, on the other hand, it can safely be asserted that even a faint skiagraphic reproduction of biliary calculi proves their presence to the expert reader. The author is confident that with increased knowledge and improved technique, the skiagraphic reproduction of biliary calculi will soon prove to have become a reliable method.

The outlines of the gall-bladder are often shown if there is cholelithiasis. On account of the long-continued irritation, the bladder walls become thick and fibrous and consequently less permeable to the rays.

The *kidney* must be skiagraphed in the dorsal position. Tubes of moderate hardness are best for their skiagraphic representation; very hard tubes penetrate the organs and leave no shade. Renal fluoroscopy cannot be relied on with our present means. Hydronephrosis and echinococcus cyst can be represented under favorable circumstances. The greatest usefulness of the rays in renal disease, however, is displayed in diagnosticating concretions. Great credit is due to MacIntyre for having been the first to skiagraph a renal calculus. Soon afterward Twain, Thyne, and Kuemmell, as well as the writer, obtained distinct skiagraphic representations of nephrolithiasis.

At first it was thought that only such calculi could be represented as consisted of hard and firm material, like oxalates, while the more penetrable urates left an indistinct shadow, and the translucent phosphates hardly showed at all. Thus the success of skiagraphy in calculi of the urinary tract seemed to depend on the chemical composition of the calculi, and, consequently, on their greater or lesser opacity. Now, with the new powerful tubes, more or less opaque shadows of the three different kinds can be obtained. The beautiful work of Abbe, Bevan, and Leonard, all of this country, furnishes a striking illustration of the immense progress of the young science in the short space of a few years.

As to the technique of the skiagraphy of renal concretion many of the principles emphasized in connection with gall-stones hold good. In regard to their chemical composition, it should be remembered that a calculus may consist of different salts. In one of my cases five layers were found, the nucleus and third layer consisting of calcium carbonate, its branches of a combination of calcium carbonate and triphosphate, and the outer crystalline layer of carbonate of magnesium and ammonium.

Under such circumstances the nucleus will be more marked if a tube of moderate hardness is used, while the branches will be more conspicuous if a softer one is employed. As a rule, tubes should be chosen that are slightly softer than those used for skiagraphing biliary calculi. In other words, they should show the carpal epiphysis of the operator's radius very dark gray. The time of exposure should be six minutes in thin, and about nine minutes in stout individuals. A good skiagraphic representation of nephrolithiasis renders an exploratory incision unnecessary. It will naturally settle the question of the presence or the absence of concretions absolutely. In case an operation is indicated, it will also give valuable hints as to the technique.

While, as has been said above, a negative result cannot be relied upon in a case of suspected cholelithiasis, a good skiagraphic plate that does not show the presence of renal calculi may safely be regarded as diagnostically conclusive. The characteristics of a reliable renal skiagraph are that it shows the outlines of the psoas muscle and the lower ribs. If they show distinctly, a calculus which is not smaller than a pea would necessarily also leave its shadow on the plate.

When we bear in mind the high mortality of nephrolithiasis at a late stage and how many lives will be saved by early operation, the importance of early recognition of the calculi becomes evident. But the only method that permits this is skiagraphy.

In interpreting skiagraphs taken for suspected nephrolithiasis, it should be borne in mind that under extraordinary circumstances bili-

ary calculi may be taken for right renal calculi. It may be said, however, that as a rule the shape of biliary calculi is different from that of renal concretions; the former are located higher up and do not show so clearly from the back as they do from the front. Of course, in those cases in which the shape of the kidney is well marked, the shadow of the renal calculus will hardly be misinterpreted. In case of doubt, a lateral exposure will show a renal calculus in the back, while gall-stones would appear in front. The clinical symptoms should also be properly considered before conclusions are drawn. Just as in cholelithiasis the skiagraphic proof of the presence of small calculi shows that much is to be hoped for from medical treatment, while the removal of large calculi cannot be expected by any other than surgical means. The distance of the tube from the plate in skiagraphic representations of the kidney should be about 50 cm.

Ureteral and vesical calculi can be skiagraphed after the same principles. Difficulties arise only in stout individuals. A vesical calculus shows best with the subject in the abdominal position, the centre of the tube to be directed to the upper margin of the symphysis pubis. Any vesical calculus, be it ever so small, will surely be evident on a good skiagraph. A lateral exposure should always be made besides, because it shows whether the stone is free or encysted. If the patient bends slightly forward in the lateral position, the calculus, if free, sinks toward the anterior vesical wall and becomes conspicuous directly behind the anterior abdominal wall. If it is not free, it usually shows far back toward the sacrum, since encysted calculi are nearly always attached to the posterior or vesical wall. If the stone is of very large size, or if a great number of them are present, the whole vesical space is filled up and displacement is not apt to occur. So far as the diagnosis of the number, shape, and position of vesical calculi is concerned, the Roentgen rays afford a much more valuable means than the cystoscope. The time of exposure should be about five minutes, or from three to four with the Wehnelt interrupter. A medium tube is best.

Foreign bodies in the abdomen are, of course, easily demonstrated. As modern surgery makes immediate laparotomy imperative in all bullet wounds of the abdomen, it may be realized how important is skiagraphic localization. Tacks and needles can be easily localized. The popularity of the Murphy button gives frequent opportunities to observe its characteristic shadow while it travels through the intestinal tract.

Tumors of the stomach are representable according to their degree of density. The outline of the stomach can be mapped out if the viscus is filled with salts, such as subnitrate of bismuth, that are impermeable to the rays. The introduction of a soft-rubber tube the lumen

of which is filled with mercury is, however, preferable. A rubber tube containing a thin, flexible steel wire in a spiral form permits the rapid representation of the outlines of the stomach. The stoppage of this tube indicates its arrival at the large curvature of the stomach, and further propulsion shifts it along the wall. There the steel spiral is clearly shown by the skiagraph.

Inflation of the stomach by carbonic-acid gas, air, or a mixture of tartaric acid and bicarbonate of soda has also been used to define its outlines. The large and small curvatures, as well as the cardia, can thus be represented. The infantile stomach is especially fit for skiagraphic representation. In selected cases, the relations, especially the motions of the spiral wire, can be studied by the aid of the screen. Tubes of medium hardness should be chosen.

The diagnosis of the various types of spina bifida has also been simplified by the rays. It was sometimes impossible to differentiate simple meningocele, myelomeningocele, and myelocystocele. Especially the distinction between meningocele and myelocystocele has been generally impossible. Considering only the one point that in meningocele aspiration should be tried first, while in the other varieties extirpation of the sac must be resorted to, the importance of the question is self-evident. The skiagraph now shows, with absolute distinctness, whether or not there is an opening in the spinal column; it usually shows also the presence or absence of nerve substance, and sometimes even its expansion in the sac. In those cases in which the presence of fibromyoma is suspected, the skiagraph gives the needed information.

The usefulness of the Roentgen rays in *gynecology* is still limited. Many trials have been made to obtain representations of the uterus, but they have always given unsatisfactory results. In a few instances, the gravid uterus and the faint outlines of the fœtus have been detected.

In obstetrics the advantages are greater, since so many important questions hinge on the condition of the pelvis. Symmetry and asymmetry of the pelvis, ankylosis, changes in the iliosacral joint, and the length of the various pelvic diameters can be well shown. In the case of a woman, aged twenty-two years, the rachitic pelvis showed an elliptical shape, which explained fully why she could never be confined in a normal way. A successful Cæsarean section has been performed on her.

If the exposures are made strictly under the same conditions, the tube being at the same distance from the plate and in the exact perpendicular direction, the measures of the conjugata vera, the introitus pelvis, and the transverse diameters can also be relied on.

After symphyseotomy it can be ascertained whether there has remained any diastasis of the pubic bones. In case there is proof of

the existence of considerable diastasis, a second operation may be avoided.

Pelvis and Lower Extremity.—Irradiation of the pelvis is best made in the perpendicular direction, the tube being held as near as possible, and the symphysis ordinarily being regarded as the centre. A dorsal as well as an abdominal exposure is necessary as a rule. The best position of the body is when the legs are slightly inverted, heavy sand-bags supporting them. When the subject is in the abdominal position, the dorsum pedis must also be supported by a sand-bag. Fractures of the pelvis can be easily recognized, and by the location of displaced splinters a conclusion can be drawn as to possible injuries of the intrapelvic organs.

Fig. 17.—Congenital Dislocation of Both Hips in a Girl of Two and a Half Years.

In exstrophy of the bladder the skiagrapher may succeed in demonstrating the extent of the symphyseal gap. The result of a plastic operation can be studied by skiagraphic observation.

In the treatment of congenital dislocation of the hip (Fig. 17) the skiagraph will determine what method of treatment should be chosen, as it reveals the relation between the femur and the acetabulum. If the condition of the latter is unfavorable, bloodless reduction will be impossible and a cutting operation must be performed. The skiagraph will also show whether reduction of a dislocated hip has been successfully effected or not.

At the early stage of inflammatory processes in the hip-joint a correct diagnosis is of the utmost importance. In doubtful cases the rays will determine whether simple, traumatic, or tuberculous coxitis (Fig. 18) is present. In view of the great difference in treatment, the immense importance of a positive diagnosis is evident. It is advisable

to skiagraph both hips, so that the healthy and diseased side can be compared.

In a normal hip-joint there is a regular semicircular light area between the femoral head and the acetabulum, while in a tuberculous hip the articular outlines, instead of being regular and marked, are irregular and diffuse. Slight projectious of the femoral head are often found at an early stage and indicate the presence of fungous granulations. Later on, cheesy foci in the acetabulum, the head, the neck, and the trochanter major can often be detected. Such processes must

FIG. 18.—Advanced Tuberculosis of the Hip in a Boy of Ten Years.

be differentiated from osteomyelitic foci, which have originated within the bone and gradually entered the joint. After the healing process is completed, the degree of atrophy of the femur and the extent of the ankylosis can be well studied.

Arthritis deformans coxæ is characterized by the skiagraphic representation of osseous proliferations from the articular outlines of the head of the femur, the shape of which sometimes reminds one of a papilloma.

It is acknowledged that in differentiation between fracture of the acetabular margin or of the neck of the femur and dislocation and con-

tusion of the hip, grave errors were formerly committed by the best surgical authorities. The Roentgen rays have made it possible to avoid these embarrassing errors. Especially has fracture of the acetabular margin, with its bad functional prognosis, been repeatedly observed, and in some of the instances the diagnosis has not been made until the rays have been used. On the strength of this more reliable information, I have been able to remove acetabular splinters with safety, thus restoring functional ability in two instances. The rays have also shown that a sharp line of distinction between intra- and extracapsular fracture of the neck of the femur cannot be drawn, and that in the so-called extracapsular variety the fracture line generally extends into the intracapsular region, and conversely that in intracapsular fracture the fracture line often extends somewhat outside the joint. The principles of treatment must be modified accordingly.

The skiagraphic proof of the presence of impaction implies the omission of many manipulations, and suggests immediate immobilization in the impacted position. The diagnosis of isolated fracture of the trochanter major will no longer be confounded with contusion.

A good skiagraph of the knee-joint illustrates its anatomical relations better than any of the beautiful illustrations in the text-books on anatomy. Being the frequent seat of simple as well as of traumatic and tuberculous inflammations, it offers many opportunities for skiagraphic differentiation. Recognition of the various injuries of the knee-joint has become much easier, since we are able to show even a displacement of one of the menisci tibiæ. Floating bodies in the knee also can be distinctly located. While the diagnosis of a fracture of the patella by the ordinary method is easy, as a rule there are instances in which contusion or impaction has been assumed, but the skiagraph has revealed the presence of multiple fractures. It must be borne in mind that the popliteal space often shows a well-defined shadow that might be taken for a bone fragment or a foreign body, but which in reality is a normal sesamoid of the semitendinosus muscle. This sesamoid is found in about eight per cent. of subjects examined.

Differentiation between bony and fibrous ankylosis is now easy. This is most important, since bony ankylosis can be remedied only by separation by a chisel, while in fibrous ankylosis forcible motions can be resorted to.

In tuberculosis of the knee the progress of healing can be observed by the rays after resection as well as after the injection of iodoform ether. While a normal knee-joint shows marked regularity of the outlines of the articular surfaces, the contours of a tuberculous knee appear irregular and diffuse. Later on, when cheesy foci have formed,

their areas become translucent. The cartilage is sometimes entirely destroyed and gives no shadow.

No attempt should be made to remove a foreign body before skiagraphic evidence is furnished.

When we realize that fractures of the leg constitute about sixteen per cent. of all fractures, and that they show a great tendency to displacement, the importance of the Roentgen rays as a controlling means during the treatment becomes evident at once.

The presence and extent of osteomyelitis, so frequently found in the tibia, can be diagnosed by the rays, the focus of disease always appearing well marked. The ease and security with which operative procedures in these cases can be carried out under the control of the rays cannot be too strongly emphasized. Formerly it was deemed advisable to chisel up the whole length of the bone in order to be sure that every possible focus had really been reached. Now the skiagraph shows exactly the length of the incision that is necessary for a thorough removal.

In cases of malunion, osteotomy is simplified by the rays. The arrest of growth of the tibia after operations for necrosis can be well studied. Rachitis and tuberculosis also offer a wide field for study in this region.

Osseous cysts at the upper as well as the lower end of the tibial epiphysis are of not infrequent occurrence. They are confounded sometimes with osteosarcoma—a most unfortunate accident, indeed, since it frequently means unnecessary amputation. From a skiagraphic study of a series of osteosarcomas to be spoken of in detail later, one feels justified in saying that in osteosarcoma the outlines of the bone are always more or less abnormal and indefinite, some areas even appearing entirely translucent; while in osseous cysts the cortex appears thin and narrow, but well marked and regular. The fluid centre of the bone is entirely translucent, the light shadow showing the same regularity. The adjacent epiphyses are normal.

It is especially the regularity of the texture of the walls of the cavity, as they appear on the skiagraph, that seems to be the characteristic feature of osseous cysts in contradistinction to the irregular texture of osteosarcoma. In further differentiation, it may be added that nearness of the lesion to an epiphysis is also in favor of osseous cyst for obvious histologial reasons.

In a case of osseous cyst of the tibia presented to the surgical section of the New York Academy of Medicine, March 11th, 1901, the skiagraph revealed the presence of a large triangular shadow, the base of which corresponded to the epiphyseal line. This triangle was surrounded by another narrow, dark, and regularly arranged shadow that represented the distended but otherwise normal cortex of the tibia.

The light shadow was interpreted as a cavity, presumably containing a fluid of some kind. The normal outlines of the fibula could be distinctly recognized through the light area, although the inner surface of the leg rested on the photographic plate. The marked regularity of the texture of the cortex, as well as the uniformity of the light shadow representing the cavity, showed that osteosarcoma was not present in this case, wherefore a conservative operation was advised, which was performed with a most gratifying result.

The *ankle-joint* and its vicinity are frequently the seat of injuries and diseases of various kinds. The history of the faulty diagnosis in this region would fill many volumes. Nowadays, differentiation between fracture, dislocation, distortion, contusion, and last but not least, inflammatory processes, is easy. The healing process, after operation for pes equinovarus and equinovalgus, can be easily studied and influenced accordingly. Most cases of so-called distortion prove to be fractures pure and simple when looked at by means of the "Roentgen eyeglass." Sometimes very small splinters are represented which are severed from the bone surface. They are embedded in bloody effusion, which prevents their recognition by palpation, so that naturally a diagnosis of "sprain" is made. Massage can seldom be borne by the patient, because the friction caused by this treatment presses the sharp splinters forcibly against the injured bone. The patient will, on the other hand, be comfortable if treated after the general principles of fracture treatment, *i.e.*, immobilization.

If there are no little bone fragments but only hæmatoma from lacerated tissue, then, of course, massage is the treatment *par excellence*, and immobilization means unnecessary delay.

Fractures of the astragalus and calcaneum were often confounded with Pott's fracture, the final surgical result naturally being very unsatisfactory. Minute anatomical knowledge is necessary to appreciate a skiagraph of these bones thoroughly. How misleading the lack of such knowledge may become is evident from the fact that the os intermedium cruris (os trigonum tarsi) has been mistaken for a fragment severed from the astragalus. This bone is a typical part of the tarsus of all mammalia, and its frequency is estimated at from seven to eight per cent. Shepherd, who mistook this bone for a fractured fragment, says: "The fact that this fracture is not mentioned in any of the text-books on surgery or in special treatises on fractures would easily be accounted for by its only being discovered by dissection; it causes no deformity, and the symptoms it would cause during life would probably be obscure." The same author tried to produce this fracture artificially on the cadaver, but "in every case," he says, "where this manœuvre was performed, I failed, even when the greatest force was used, to break off a little process of the bone mentioned

above." Pfitzner regards the os trigonum tarsi as an integral part of the posterior process of the astragalus in the adult, which is analogous to the os intermedium antibrachii. Fig. 19 shows a normal os intermedium cruris at the posterior aspect of the astragalus. This condition was detected accidentally when the patient was skiagraphed, after

FIG. 19.—Splintering of the Ossa Cuneiformia in a Boy of Seventeen Years; the figure also shows a normal os trigonum tarsi.

his foot was crushed by an elevator. The ossa cuneiformia were shattered.

The isolated fracture of the other tarsal bones was seldom recognized in a living person prior to the discovery of the Roentgen rays.

The foot is easily skiagraphed in the direction of the dorsum toward the planta pedis from the toes up to the upper third of the metatarsus. But farther back the first and third cuneiform bones and the scaphoid offer an obstacle, so that it is necessary to skiagraph these portions transversely by having the outer surface rest on the plate. It is by this procedure only that the isolated shadows of the astragalus, the

calcaneum, the os cuboideum, the scaphoid, and the fourth and fifth metatarsal bones can be distinctly outlined so that false interpretations can be excluded.

It is generally accepted that the superficial location of the metatarsal bones makes the recognition of their fractures easy. Still, while this may be true of the first and fifth metatarsal bones, on account of their accessibility, the dense tendinous and ligamentous tissues overlying the second, third, and fourth metatarsi are apt to veil the fracture signs within their tract. The difficulty of differentiation is much greater when, as is the rule, the fracture is associated with injuries of the soft tissues causing œdema and swelling.

How often metatarsal fracture has been overlooked can be estimated by the fact that, before the discovery of the Roentgen rays, most cases of fracture of the second or third metatarsal were mistaken for pathological change in the soft tissue—in the German army known as "foot œdema." It was reserved for the Roentgen rays to disclose the fact that this much dreaded condition was a fracture pure and simple, and that it was produced by overburdening the marching soldier.

The text-books treat metatarsal fracture as a stepchild, most of them saying that it requires neither detailed description nor any special mode of treatment. A few say that if there is any displacement it will be toward the dorsum of the foot. Only Hoffa alludes to the possibility of plantar displacement also. But nowhere is reference made to the lateral displacement, which we regard as of not infrequent occurrence, and also as an important complication since it is always followed by considerable functional disturbance. The fact that the lateral displacement was never recognized before explains fully why efforts of reduction have been neither made nor advised; consequently the fragments, left to themselves, whether in a general immobilizing dressing or not, unite in a deformed position, and bony enlargements, as well as functional disturbances, are the result. The œdematous feet of persons who must work hard, or march, or stand on their feet during the whole day furnish a striking illustration of the consequences of badly united metatarsal fractures, as they are disclosed at the present time by the Roentgen rays. It is obvious that the more accurate and varied are the diagnoses that these rays enable us to make the greater difference there must be in our plans of treatment. Previous experiments have shown that metacarpal fragments are invariably held in place by elastic pressure. The same principles obviously apply to metatarsal fracture.

The sesamoid below the head of the first metatarsal bone is sometimes fractured by direct violence, a fact that was also never before recognized. The various osseous changes of the foot in acromegaly are an interesting subject for skiagraphic study. The phalanges ap-

pear broader and thicker than normal and show no osteophytes. The metatarsi also show massive structures. The pathological anatomy of hallux valgus and that of arthritis of the large toe are also much better appreciated and judged since the advent of the rays. Skiagraphs of the toes are frequently serviceable in the detection of foreign bodies, especially of needles and headless tacks. Malformations, like syndactylism, etc., can also be well studied. The exact anatomical diagnosis that we are now able to make enables us to determine whether surgical interference is possible, and if so, it outlines clearly our *modus operandi* beforehand.

To avoid false interpretations of skiagraphs of children, it should be remembered that the lower epiphyses of the tibia and the fibula show their osseous nuclei in the first and second years, and unite with the diaphysis between the eighteenth and the twenty-fifth year, or according to skiagraphic evidence, sometimes even before the eighteenth year. The osseous nuclei of the astragalus and of the calcaneum appear *intra utero*, that of the cuboid shortly before or after birth, that of the cuneiform between the first and fifth year, and that of the os naviculare from the first to the fifth year. The osseous nuclei of the metatarsal bones and of the phalanges appear from the second to the tenth year, and unite with the diaphysis between the sixteenth and the twenty-second year.

Shoulder and Upper Extremity.—Irradiation of the shoulder is best made perpendicularly, the tube being as near as possible and the glenoid cavity being regarded as the centre. An abdominal posture is necessary as a rule. Children require between three and four, thin adults about six, and stout adults seven to eight minutes' exposure.

A good skiagraph of the shoulder-joint is best obtained from the anterior aspect, in other words, in the abdominal position. The sigmoid form of the clavicle must appear well marked. The scapula is best studied posteriorly, that is, in the dorsal position. Its triangular shadow can be well differentiated from that of the ribs. Its spine can be followed in its course, running parallel to the clavicle and ending at the acromion. The acromioclavicular junction shows a hiatus which in the early days of skiagraphy was mistaken for a diastasis of the joint. An increased knowledge has taught that this apparent diastasis is by no means pathological and that there is a normal gap between the osseous ends of the acromion and the acromial end of the clavicle. The glenoid cavity, containing the head of the humerus, and the major and minor tubercula should also be well marked. Between the clavicle and the scapular spine appears the dark shadow of the coracoid process (Fig. 20).

Tumors of the clavicle can be differentiated by skiagraphy. Atrophy of the clavicle in aortic aneurysm can be represented. The true

character of pulsating tumors, erroneously taken for subclavian aneurysm, may also be shown (see Fig. 14). Tuberculous foci are sometimes found in the clavicle. It is needless to say that dislocation of the clavicle is easily differentiated from fractures by the aid of the rays.

Skiagraphy of the scapula is indicated in tumors, especially in osteosarcoma.

Sometimes the shaft of the humerus is the seat of a periostitic process or of an osteomyelitic focus. In such cases a preceding trauma is often reported. The pain, the œdema, the fever, and the general

FIG. 20.—Non-displaced Fracture of the Humerus. Back view, showing separation at the anatomical neck. The front view of the same case shows that it is an intertubercular fracture.

debility may be sometimes so little marked that differentiation becomes difficult. The skiagraph not only removes the difficulty of diagnosticating this disease, the true etiology of which is still so obscure, but also furnishes a trustworthy guide for the operative technique at the same time. In the case of a young girl the slow onset of the symptoms did not seem to be in favor of an acute inflammatory process. Pain being present only temporarily, the fear of a malignant growth was apparently not unjustified. The skiagraph at once did away with all anxiety, since it revealed the presence of a circumscribed osteomyelitic focus at the middle of the humerus. The focus was

easily exposed by the chisel under the mentorship of the skiagraph. That the skiagraph had also spoken the truth by demonstrating the integrity of the remaining portions of the humerus was shown by the speedy recovery.

The median as well as the radial nerve may become lacerated by the splintering of the bones. This requires immediate neurorrhaphy. Of course, the nerve fragments cannot be represented by the rays, but the location and the character of the fracture, in conjunction with the symptoms in the sphere of these nerves, establish the diagnosis and dictate the operative steps.

In children the skiagraphic anatomy of the elbow-joint may be falsely interpreted. It should be remembered that the osseous nucleus of the interior of the capitulum humeri appears between the second and third years. Another nucleus shows in the internal epicondyle at the fifth year, a third in the trochlea between the eleventh and twelfth years, and soon afterward a fourth in the internal epicondyle. The nucleus of the internal epicondyle unites with the diaphysis between the sixteenth and twentieth years; but the other three nuclei form a synostosis among themselves at the seventeenth year, then constructing the uniform osseous epiphysis which completes its synostosis with the diaphysis at about the twentieth year.

In very young children the eminentia capitata appears as if entirely severed from the humerus, although the relations are normal. The explanation of this important phenomenon is that the epiphyseal tissues are not sufficiently ossified to produce a shadow on the plate. If these points are not thoroughly considered the diagnosis of a displaced fracture fragment might be erroneously made. The lower epiphysis of the humerus consists of four nuclei, which do not ossify until from the eighth to the seventeenth year. The epiphyses of the trochlea and of the olecranon do not ossify until between the seventh and the twelfth year, which explains why an osseous nucleus is still connected with its neighboring epiphyseal nuclei; and why the diaphysis, connected by cartilaginous tissue, appears as an isolated piece of bone, which might erroneously be taken for a fragment.

It must also be borne in mind that in fractures in childhood the process of ossification is influenced by various affections of the bone, such as rachitis, for instance.

As stated before, inflammatory processes in the elbow-joint are to be viewed from the same points as those of the knee-joint.

Tuberculosis of the carpus, metacarpus, and phalanges, frequent in children, can be well studied and treated under the guidance of the rays.

It was the writer's privilege to discover a pathological condition (tenontitis and tenontothecitis prolifera calcarea) which, so far as he

knows, has never before been described. It was in the person of a Russian tailor, forty-two years of age, who had noticed a small and painless swelling formed in the dorsal surface of his right hand eleven years before. This swelling increased gradually, but until it grew painful no medical advice was sought. At the first examination a globular tumor was noticed on the dorsum of the right hand, of the size of a moderately large apple. Its surface was red, its consistence irregular, some parts of it being hard, while others appeared soft to the touch. The centre of the tumor was occupied by a large ulceration, which was surrounded by several fistulous tracts from which turbid sero-pus issued. The first impression was that the tumor represented an osteosarcoma, and it was feared that speedy amputation would be indicated. It was decided to make use of the Roentgen rays, which proved to be a valuable means of information, since the true condition was at once precisely defined. A skiagraph which was taken by means of a long exposure showed that the third metacarpophalangeal joint was the seat of a focus of inflammation. The first phalanx was grown together with the metacarpus. The cortex of the condylar side was totally destroyed, appearing as if scooped out with a gouge. By faint irradiation the limits of the tumor were well outlined. A third skiagraph taken under powerful irradiation and a short exposure showed the bones faintly, but permitted distinct recognition of the various shadows of the tumorous portions. The light areas showed the suppurating portions while the dark shadows corresponded to the calcareous areas. These, as shown also by the subsequent operation, were the predominating elements of the tumor. It now became evident that there was a chronic inflammatory process probably of a tuberculous nature.

Extirpation showed the defect of the bone filled with yellow cheesy masses, the synovial membrane being partially destroyed at the same time. But the most surprising feature of the condition was that the extensor tendons of the digits, excepting the thumb, appeared as if cemented into one mass of mortar. In dividing this mass the knife caused a loud grating sound. Of the tendon on the third finger only a few rudimentary fascicles had remained, so that it had to be sacrificed entirely. The fascicles of the second and fourth extensor tendons were kept apart by the concretions. They were, in fact, so much incrusted that only a small portion could be felt. The weight of the whole amount of the calcareous mass removed proved to be 80 gm.

Microscopical examination showed round-cell granulations and the presence of staphylococci, but no evidence of tubercle bacilli. There were also deposits of phosphates and carbonates of calcium. The fragments of the tendons showed granulation of the circumfascicular and intrafascicular connective tissues. Hæmatoxylin stained the degenerated tissue dark brown violet, and picrocarmine changed it to red.

Recovery was slow and was not perfect until six months after the operation.

Now, what was the integral character of the disease? There was a much degenerated (cheesy) tissue in the state of necrobiosis which seemed to have a sort of magnetic effect, so to speak, on the dissolved calcareous salts, inducing them to amalgamate. Such petrifactions are found in tuberculous (cheesy) foci of the lungs and not infrequently in endocarditis, pericarditis, old pleuritic bands, uterine myomata, and renal epithelium. The author has been able, by means of the Roentgen rays, to define the mode of petrifaction in the walls of blood-vessels as well as in the degenerated thyroid gland.

The tendons and their sheaths seem to be but seldom the seat of predilection for calcareous deposits. Still, with the increasing popularity of the Roentgen rays, more light may also be thrown upon the pathology and significance of this hitherto unknown disease for which the writer suggested the name of tenontitis and tenontothecitis prolifera calcarea (*New York Medical Journal*, April 27th, 1901).

As previously mentioned, the great scientific and practical value of the Roentgen rays is also evident in the study of congenital malformations of the bones. Skiagraphy of the extremities especially has given more valuable information than dissection. The exact anatomical diagnosis that it enables us to make informs us whether surgical interference in a case of malformation is possible, and if so, outlines clearly our *modus operandi* beforehand. The ingenious operations of Bardenheuer (division of the ulna for carpal implantation) and of von Eiselsberg (transplantation of the toe), and the work of Kirmisson, Vulpius, Middleton, Pagenstecher, von Bardeleben, Joachimsthal, Schede, Lambertz, and Grünmach furnish most brilliant testimony to our progress in this direction.

Fortunately the most frequent abnormality is the one that can be easily remedied, namely, polydactylism. If there is but a rudimentary finger attached loosely by a pedicle and containing no phalanges at all, removal is very simple. But when, as is the rule, there is a true supernumerary digit articulating with another phalanx or the head or side of a metacarpal bone, the site of exarticulation must be well known before the operation. Otherwise, the better developed phalanx may be sacrificed.

Syndactylism, while not so frequent as polydactylism, also represents a large group of cases of malformation of the upper extremity and is likewise amenable to operative interference.

Congenital deficiencies are naturally much less amenable to correction. But that surgery is not without resources even in desperate cases of this kind is made evident by the transplantation of a toe to the hand, successfully undertaken by von Eiselsberg.

In brachydactylism, combined with ectrodactylism, the Roentgen rays have proved to be of great value.

Foreign bodies are easily shown in the hand, especially needles in the palm, a condition so often coming under the observation of the general practitioner.

Inflammatory Processes, Neoplasms, and Other Affections of the Bones.—The Roentgen rays have opened entirely new fields in differentiating the various inflammatory processes from the growths of the bones and joints. If they cannot always give positive information, they often, by the method of exclusion, increase the chance of arriving at a correct diagnosis.

If in a case of an obscure swelling of the knee-joint, for instance, the Roentgen rays reveal no impairment of the integrity of the joint, osteitis, tuberculosis, syphilis, and bone injury can be excluded; it will be certain then that only the soft tissues are involved. Thus we may, in conjunction with other clinical symptoms, be satisfied that we have to deal with a rheumatic swelling. But in many instances the Roentgen rays give positive information.

Again, in periosteitis as well as in osteomyelitis the skiagraphic signs are well marked. Abscesses can not only be localized, but their extent can also be so well outlined that the technical steps of the operation can be definitely traced in advance. The feeling of security the surgeon has while proceeding under the mentorship of the skiagraph gives a satisfaction unknown in former years, when often the whole femur, for instance, had to be exposed in order to ascertain whether all the foci had been detected. If the Roentgen rays show but one focus, no other regions of the bone need to be attacked. In such cases a preceding trauma often opens the avenue of infection. The pain, the œdema, the fever, and general debility may be sometimes so little marked that differentiation becomes difficult. The skiagraph not only removes the difficulty of diagnosticating this disease, the true etiology of which is still so obscure, but also furnishes a trustworthy guide for the operative technique. Osteomyelitis is of a decidedly infectious character, generally due to the entrance of the staphylococcus into the blood circulation. Fortunately, this bacterium has a tendency to induce the formation of circumscribed foci in the vascular tissues of the bone, viz., the medulla and sometimes the periosteum. The predilection of osteomyelitis is for the long bones of young individuals. It is self-evident, therefore, that the early recognition of osteomyelitic foci renders the prognosis of their evacuation extremely favorable. The osteomyelitic focus is distinguished by its light shadow in the midst of the dark shadow of the cortex. The regularity of the cortical line distinguishes it from osteosarcoma, and the absence of distention from osseous cyst.

Necrosis and other later stages of inflammatory processes can be represented still more distinctly. The size and shape of sequestra can be well made out (Fig. 21). It can furthermore be ascertained how they are located in their bony coffin, and whether they still adhere or are exfoliated. Under the guidance of the Roentgen rays extraction is very easy. The regeneration of osseous tissues can also be well studied in such cases by the skiagram. Foci of the same character are sometimes formed in typhoid fever. They have to be treated after the same principles.

FIG. 21.—Necrotic Bone Free in the Centre of the Left Femur, and a Large Sequestrum at its Outer Aspect, in a Boy of Seven Years.

In skiagraphy of inflammatory processes in the joints, as in the case of acute rheumatism, the integrity of the articular outline is well marked. The same applies to acute inflammatory processes due to infection. In the latter event the distention of the joint by the serous or purulent effusion may be represented by the skiagraph. In chronic rheumatic processes the articular bone-line appears somewhat irregular.

In arthritis the contours of the bone epiphysis appear irregular, and show indentations on some portions, while others are veiled. The arthritic deposits are recognizable as light shadows of the deformed epiphyses, as they consist of translucent uric-acid salts, while their periphery is distinguished by a dark sphere.

In cases of gonorrhœal arthritis of the wrist the structures of the carpal bones appear extremely light, and their contours irregular. They can, however, be represented only by using a soft tube, since the rays from a hard one would penetrate the deposits to such an extent that they would leave no impression on the photographic plate. I take this opportunity to call attention to the necessity of employing soft tubes in general for the representation of osseous diseases of the hand, forearm, foot, and leg.

In arthritis deformans the osteitic proliferations are especially

abundant, and are well shown by the rays. The skiagraph reproduced in Fig. 22, of the elbow of a laborer fifty years of age, revealed the presence of malunion (lateral displacement) of the coronoid process of the ulna, which probably had given the first impetus for the development of the arthritis deformans, which is especially well marked in the external condyle of the humerus. The left condyle showed synostosis with the olecranon.

In the arthropathies of tabes dorsalis the bone appears eroded, as in osteoperiosteitis, but at the same time it is considerably distended.

In tuberculosis of the bones and joints the Roentgen rays not only give information as to the seat and extent of the tuberculous area, but also offer sometimes the only means of differentiation from other affections. The walls of an intraosseous focus appear thickened. Some portions are translucent and their contours irregular. The articular outlines of a tuberculous joint have lost their regularity and appear diffuse, cloudy, and sometimes shaggy. In late stages, when cheesy foci have formed, for instance, the areas appear translucent. The cortex is sometimes entirely destroyed and leaves the impression of having been scooped out with a gouge. When there is calcareous degeneration the foci appear in dark shadow.

In cases of extensive tuberculous destruction the eroded and displaced cartilages can be studied. In tuberculous coxitis the spontaneous upward dislocation of the femur and the separation of its head in the acetabulum can also be well recognized.

FIG. 22.—Arthritis Deformans, Developing after Fracture of the Coronoid Process of the Ulna.

It need not be said that the early detection of a tuberculous focus enables the surgeon to do a conservative operation, while in a late stage of extensive destruction such efforts are futile.

Cheesy foci of cervical and bronchial glands have also been re-

produced by the author distinctly when they contained calcareous deposits.

By realizing that so-called osteosarcoma is the most frequent of morbid osseous growths, and that of all tumors sarcoma offers the gravest prognosis, the importance of a thorough diagnosis need not be emphasized. The matrix of osteosarcoma, like that of all osseous growths, is either the periosteum or the medulla, in combination with the tissue originating from the proliferation.

Periosteal sarcoma is of a moderate hardness, and contains either round, or spindle, or polymorphous cells. It attaches itself to the bone laterally, but may in its further development encircle it entirely. It may develop into real osteosarcoma at a later stage when osseous trabeculæ are formed. The skiagraph of periosteal sarcoma is characteristic, since it shows fine spiculated trabeculæ which radiate from the surface. Periosteal sarcoma spreads rapidly and is highly malignant. Whenever the diagnosis is made, amputation should be insisted upon.

Sarcoma originating from the medulla is called myelogenous, and is of a less malignant character. It may be classified as soft, hard, alveolar, and multiple. The soft myelogenous variety shows the ordinary texture, the predominating feature being the presence of round cells. It has a decidedly more benign character than the periosteal type, and therefore justifies a conservative attempt, that is, extensive extirpation. Spontaneous fracture may be produced by the carious destruction of the spongy portion. At a later stage the osseous shell will yield, the sarcomatous tissue spreading in every direction.

This variety has a predilection for the long bones, especially their ends, and predominates at the lower epiphyses of the femur, tibia, humerus, and radius. Skiagraphs of the soft myelogenous variety show the absence of osseous tissue, although small fragments of it are sometimes left here and there.

The hard myelogenous variety, generally called endosteal or central sarcoma, also shows the ordinary sarcomatous structure. But its distinguishing feature is its fibrous texture and the presence of spindle cells. Some portions contain various tissues, the spindle-cell tissues often containing giant cells. If smaller or larger bone trabeculæ are produced it is called osteosarcoma proper; if there are calcareous deposits, petrifying sarcoma; and if the tissues become vascular, telangiectatic sarcoma will be formed which may be mistaken for an aneurysm. In later stages, when there is a regressive metamorphosis, fatty or cystic degeneration may take place. Then neoplasms, which occur especially in the femur, tibia, and inferior maxilla, may attain an enormous size. The skiagraph of osteosarcoma proper shows more osseous tissue than the periosteal variety, but its outlines are very irregular. They usually commence near the epiphysis of a long bone.

Fig. 23 shows osteosarcoma proper in a woman of forty years. The destruction of the lower third of the radius and of a large portion of the carpus is seen. Resection was performed more than four years ago. The perfect result was illustrated by a later skiagraph, which

FIG. 23.—Destruction of the Lower Third of the Radius by an Osteosarcoma.

showed a slight and most uniform atrophy of the whole left hand. In a third skiagraph, which was taken more than four years after the operation, the regeneration of the osseous tissue can be well studied.

The alveolar variety is characterized by its alveolar stroma, which

contains nests of large cells. This form has a predilection for the bones of the skull and the trunk.

The multiple variety (also called myeloma), characterized by the presence of numerous whitish foci, consists of small round cells. It has the same structure as the lymphoid sarcoma. It is nearly exclusively found in very old individuals, for whose skull and trunk it shows the same predilection as the former variety.

The skiagraph of the alveolar as well as that of the multiple type shows the foci as light irregular shadows. Their structure, their manner of destroying the preëxisting bone tissues, their thin osseous

FIG. 24.—Multiple Syphilitic Exostoses on the Humerus, Clavicle, Scapula, and Ribs.

walls, and their trabecular formation furnish the standpoint for their skiagraphic study. Osteoporosis of the trabeculæ means decalcification of the bony portion affected, which explains their foggy shadows. Intraosseous tension is responsible for the expansion of the compact osseous layer, which is thus made gradually weaker, and at last almost entirely disappears. Thus we see that it is the abnormal and indefinite outline or even the entire absence of the osseous cells, the cortex especially disappearing, which is more or less characteristic of the various types of osseous sarcoma in contradistinction to other bone diseases.

In chronic osteoperiostitis the walls appear irregular, too, but the irregularity is one-sided, and there is a globular or spindle shape. In

tuberculosis the shadow would be cloudy or shaggy. In osteomyelitis the cortex shows nearly normal outlines.

The skiagraphic expression of syphilis is characteristic also, exostosis especially being present (Fig. 24). In the congenital form large ossified areas are recognized in the epiphyses, which would appear translucent in their normal cartilaginous condition. On the other hand, light areas are noted in the diaphysis as an expression of insufficient calcareous deposit. The synostosis between the cartilaginous epiphyses and the diaphyseal end appears as a very marked line, indicating the abundance of calcareous salts deposited there. Gummata show regular light-shaded foci. Their disappearance after the administration of iodide of potassium confirms the diagnosis.

Osseous cyst showing the same clinical signs as osteosarcoma may easily be confounded with it. But in osseous cyst, while there is the same bulging as in osteosarcoma, the line of the cortex, on account of its thinness, appears narrow, but well marked and regular. The fluid centre of an osseous cyst renders the skiagraph translucent, the light shadow showing the same regularity. The adjacent epiphyses are also normal in osseous cyst. The treatment of these various affections being different, the importance of a correct diagnosis is evident. Osteomyelitis, necrosis, tuberculosis, syphilis, and osseous cyst demand conservative measures, while sarcoma calls for the most radical treatment.

The grave prognosis of sarcoma arms the surgeon against any feeling of sentimentality. Under such fatal circumstances he may not shrink from advising one of the most mutilating operations, because he knows that otherwise not only a limb but also a life will surely be lost. On the other hand, how painful must it be for a surgeon to find that because of his error of diagnosis such radical steps have been taken unnecessarily; that, in other words, an extremity may have been amputated when only an osseous cyst existed, which could have been cured by simple incision.

The fact that the interior of an osseous cyst is filled with opaque blood serum and that its walls are lined with a smooth coat, while in osteosarcoma solid masses are formed, indicates that an exploratory incision combined with microscopical examination would clear the question of diagnosis. But the Roentgen rays give us more valuable information than the exploratory incision itself, and for the patient a photographic exposure is certainly more agreeable than an exploratory examination. Should an operation be decided upon, the microscopic examination can then be made. The correctness of the skiagraphic diagnosis was proven in two of the author's cases (shown to the surgical section of the New York Academy of Medicine, March 11th,

1901). In both instances amputation had been advised because the diagnosis of osteosarcoma had erroneously been made.

At the early stage, osseous cysts, whether of the tibia or of the femur, are easily overlooked, the symptoms being insignificant. Sometimes there is very slight pain, which comes and goes. The joints are freely movable, and neither inspection nor palpation reveals any abnormality. After months the circumference of the extremity may appear very slightly enlarged, but it may not be until a fall on the thin shell of the cortex produces a fracture that the symptoms are fully appreciated.

Other osseous diseases, like osteoma, osteomalacia, and chondroma, also offer some skiagraphical peculiarities in proportion to their various textures.

It is of course necessary to know the skiagraphic features of the normal bone well, the main characteristics of which are the regularity of its shadows. The spongy portion, on account of its large amount of calcareous deposits, produces a darker shadow than the medulla.

Osteoma shows the shape of the osseous deformity (see Fig. 10), but there is the normal architectonic structure, while in osteomalacia, on account of the dissolution of the calcareous shadow, the whole bone appears translucent. In a case of old pyothorax the author was unable to obtain a skiagraphic representation of the ribs, which he was inclined to attribute to a fault of technique until repeated resection showed the presence of costal osteomalacia.

The presence of multiple exostoses leads to a suspicion of hereditary syphilis, when all the symptoms are wanting. In the case of a boy of five years, whose history was negative, the skiagraphic evidences of hyperostosis of the clavicle, scapula, ribs, humerus, femur, tibia, and fibula were the only signs present at the time (Fig. 24). The skiagraphic diagnosis was verified by the success of the antiluetic treatment.

In chondroma there is a regular light-shade area in accordance with its cartilaginous character.

In acromegaly the phalanges of the hand are broader than normal, and show no osteophytes, while their epiphyseal ends are thickened, the long bones appearing straighter and broader than normal. Some the carpal as well as tarsal bones are distinguished by the presence of of exostoses.

Similar osseous and articular changes are found in the so-called *osteoarthropathie hypertrophiante pneumique.*

In myxœdema the epiphyseal lines of the long bones are hypertrophied and show rich osseous proliferations, which, however, contain but few calcareous salts.

The changes in rachitis, on account of the absence of calcareous

deposits, are characteristic. They resemble those of osteomalacia, from which rachitis is distinguished by the irregular arrangement of interspersed osseous structures as well as by the deformed shape of the bones. In cretinism similar conditions are found, the epiphyses being nearly invisible, while only the diaphyses show distinctly.

In Raynaud's disease the nutrition of the bones is much more disturbed than is assumed. The Roentgen rays clear up at least one feature of this obscure vasomotor lesion. In one case the skiagraphs showed slight atrophy of the upper end of the third and osseous proliferation at the upper ends of all the second phalanges. The third phalanges appeared triangular and resembled claws. The same skiagraphic features were found in a man of thirty-one years and in a woman of forty-nine years ("The Roentgen Rays on Raynaud's Disease," *American Journal of the Medical Sciences*, November, 1901).

The skiagraphic characteristics described are not expected to serve as substitutes for our well-tested clinical methods of diagnosis, but should be regarded as valuable adjuncts in general, and sometimes as determining factors in doubtful cases.

ROENTGENOTHERAPY.

Roentgen-Ray Burns.—While Roentgenotherapy has not yet gone beyond the experimental stage, it has established a series of new and most important facts, which are well worth attracting the attention of the medical profession.

The peculiar integumental changes which manifest themselves in some cases after exposure to the Roentgen rays naturally suggest that they are due to a specific influence; that this influence is not due to the electric discharges, but is of its own kind, needs no further discussion nowadays.

It is only partially explained in what manner this specific influence, sometimes resulting in burns, exerts itself. It is analogous to the integumental change produced by sunlight, caustics, and acids. It is largely dependent upon the strength and the amount of the Roentgen rays. The tissues are influenced differently by different rays, just as the photographic plate is impressed differently by various kinds of light. The sensitized coating of a photographic plate not only reacts the more intensely the stronger and longer it is exposed to the light, but it also shows different impressions according to the different refrangibility of the rays of light. Thus the solar spectrum scarcely affects that portion of the plate, even in long exposure, where red is projected, while blue light and violet light leave intense impressions. Green and yellow produce stronger impressions than the red light. The more refrangible the rays are the more they are absorbed by the

bromide of silver of the photographic plate. By comparing the human integument with the sensitized plate we learn to appreciate the specific influence of the rays on it.

We may, just as in ordinary burns, distinguish three different degrees. The first degree is characterized by the symptoms of hyperæmia. Epidermis and cutis are infiltrated and the temperature is somewhat higher. Exfoliation takes place in small scales. The most pronounced subjective symptom is a tormenting itching in the skin.

FIG. 25.—Second Degree of Roentgen-ray Burn. Bullous form of *x*-ray dermatitis.

Effluvium capillorum, which manifests itself as a rule without producing any visible signs in the integument, belongs in the same category. It seems that there is a regressive metamorphosis (atrophy) of the differentiated elements of the skin, viz., the glands, hairs, and nails.

The main feature of the second degree consists in the formation of blisters, the clear or yellowish contents of which lift the corneal from the mucous stratum of the rete Malpighi (Fig. 25). The inflammatory signs are well pronounced, the tension is considerable, and the pain is intense. After the removal of the blisters the corium is exposed as a red and sore surface (bullous form of Roentgen-ray dermatitis).

The third and gravest degree is characterized by the escharotic destruction of the irradiated tissues. They show the signs of dry gangrene and their appearance is brownish-black. If they exfoliate by a slow suppurating process, or if they, as they should properly be, are removed by the surgeon, a granulating ulcer remains, the

cicatrization of which may take months (necrotic form of Roentgen-ray dermatitis).

The most characteristic difference between ordinary burns and the integumental changes produced by the Roentgen rays is that the latter do not manifest themselves before the lapse of a period of incubation. This stage, which we may properly call the latent, lasts about ten days in the simple type of Roentgen-ray dermatosis. Then the integument becomes hyperæmic. At first there is light, later dark redness, and finally the skin becomes brown and scaly. After a few weeks there is complete recovery, though sometimes slight pigmentation of the integument remains.

In the bullous type of the Roentgen-ray dermatitis intense reaction takes place after an incubation of about two weeks. This is of a subjective as well as of an objective character, and lasts about as long as the period of incubation did. Then cicatrization takes place. If the area of the irradiation was covered with hairs, depilation takes place. The process of regeneration of hair is slow, and pigmentation and teleangiectasis nearly always remain.

The necrotic type of the Roentgen ray dermatitis develops a few days later than the bullous form as a rule, and requires months for its cure. This type reminds one of the stationary form of gangrene, which is known as "glacier-gangrene" in Europe. The antediluvian face of the old inspector of the ice-grotto at the Eiger glacier in Switzerland, well known to many medical tourists, affords a real study of this interesting kind of tissue change.

While in Europe recently, the author had an opportunity of studying the hands of some roentgophilic colleagues, which presented the chronic type of Roentgen-ray dermatosis. The integument was wrinkled and shrivelled; the nails were horny and cracked, and the phalanges were thickened, so that there was tension during movement. The elasticity was lessened and the sensibility increased. Effluvium capillorum was an invariable accompaniment. Undoubtedly there was a cumulative influence. Fig. 26 illustrates this chronic type of Roentgen-ray dermatosis in the skin over a tuberculous knee after the twenty-fourth irradiation.

In studying the effects of the Roentgen rays on the integument and trying to draw conclusions for therapeutic indications—in other words, to understand their physiological significance—we must begin with a careful clinical observation of the various kinds of Roentgen-ray dermatitis.

The details of the changes which take place in the deeper tissues of the body while permeated by the rays will be considered later. It may be said, however, that a series of clinical signs have been reported, resembling those of sunstroke, as the consequences of moderate irradia-

tion, the predominating symptoms being giddiness, vertigo, palpitation, headache, and vomiting or colicky pain.

After long irradiation of course changes of tissue are to be expected. We will touch upon the question of these changes in general below and consider here only the signs of integumental change, as the paradigma of the effect of the Roentgen light.

FIG. 26.—Chronic Roentgen-ray Dermatitis.

Since February, 1896, the writer has made over ten thousand examinations with the rays; among them are nearly five thousand skiagraphic exposures, and until July, 1901, he could pride himself on never having burned any of these numerous patients, some of whom were in a rather precarious state. In his treatise on fractures he reported two cases of effluvium capillorum; in both instances the skull was irradiated often and at short intervals. Both individuals were blondes. In one of the cases depilation began after the fifth and in

the second one after the sixth exposure. After three weeks complete restoration had taken place. No disturbances of any kind remained.

In spite of the most liberal manipulation of the armamentarium he was never affected himself by the rays, so that he was inclined to imagine at last that there was a certain immunity. But when handling powerful tubes in connection with large electric dosages, he one day noticed an intense burning sensation on the dorsum of the right hand. It was the surface which used to be turned toward the Roentgen tube while the strength of the light was tested through his own wrist. The burning was accompanied by a most distressing tension, which was intensified by every motion. At first the hand appeared erythematous. Later on it became terra-cotta like and then the epidermis exfoliated in small scales, so that it resembled leather. Perspiration ceased entirely. During the sultry days of summer the distress was especially great. The left hand was now substituted for the fluoroscopic control, the right one being protected with a tinfoil glove, and the violent symptoms disappeared. Soon, however, the same signs developed at the dorsum of the left hand in a somewhat milder degree, so that he was finally condemned to complete abstention from the Roentgen rays. Since he has restricted himself to the most necessary manipulations only and remained a fair distance from the light as long as fluoroscopic control could be dispensed with, no disturbances have been felt and the appearance of his hands is again perfectly normal.

About the same time he observed the first case of the bullous form of Roentgen-ray dermatosis in a man of thirty-eight years, who in the course of two years had to submit to five thoracotomies for pyothorax. In view of the thickened pleura, which lined the immense pyothoracic cavity, he had resorted to pleurectomy, and a few weeks later the Roentgen rays were expected to give information as to the extent of the cavity as well as of the rib resection.

At first soft tubes were employed, the use of which gave but little contrast. Although a large pleural portion was removed, still a considerable part of thickened pleura had remained, which veiled the image of the ribs. After having repeated his unsatisfactory efforts seven times, he resorted to hard tubes, which gave a splendid picture, but at the same time were responsible for the development of a bullous dermatitis. The incubation lasted ten days, the skin was light red first and then dark red. Later on a blister the size of a large hand formed, the contents of which consisted of serum. After the blister was removed an excoriated surface was exposed, which cicatrized under a xeroform dressing in three weeks. Fig. 27 illustrates the pigmented integument and indicates the presence of a few telangiectatic areas two months after healing of the dermatitis. The patient is of blond complexion.

Shortly afterward the same accident happened in a blond man of twenty-five years, who had suffered from traumatic lung abscess for three years. In trying to measure the various distances of the walls of the cavity five exposures were made. Thirteen days after the last exposure a blister of the size of the palm of the hand appeared on the anterior thoracic wall, opposite the opening of the cavity. The contents of the blister consisted of serum of light yellowish color. After the opening and removal of the blistered tissues a superficial non-suppurating excoriation remained, which cicatrized under the application of a ten-per-cent. xeroform-lanolin ointment. Fig. 28 shows the excoriated surface three days after the first symptoms of the dermatitis had appeared.

FIG. 27.—Telangiectatic Areas after Roentgen-ray Dermatitis.

In both cases individuals were concerned the vitality of whose tissues had been lowered by exhaustive processes which had lasted for several years. In both instances suppurating cavities were irradiated with powerful tubes, which seem to be apt to impair the resistance of the superimposed structures. In spite of this fact pathological changes manifested themselves only after many and prolonged irradiations.

In a third case the long-continued influence of a plaster-of-Paris dressing in connection with axillary folliculitis was sufficient reason for the lowering of the vitality of the integument.

Whether in cases like these an idiosyncrasy exists has not yet been proven, but clinical observation is in favor of the assumption. So, for instance, should the author's immunity, lasting for more than five years, be considered in contrast to the dermatoses originating in others after a few months' employment only. Blond individuals seem to be

especially predisposed, all the writer's patients having been of light complexion. We may also assume that children, weak individuals, and patients like those described react quicker and more intensely. It also seems that certain regions of the body are especially predisposed.

No doubt the prolonged influence of the Roentgen rays can produce a more or less intense hyperæmia in any part of the human body. In experiments of long duration, conducted by reliable investigators, not only hyperæmia and swelling of the conjunctivæ, but also retinitis and contraction of the pupils have been observed. Thus we can readily understand that hyperæmia takes place in internal organs if the powerful influence lasts long enough.

Attempts have been made to approach this important question by experiment on the lower animals. Thus Tarkhanoff (*Gazzetta degli Ospedali*, March 4th, 1897) observed that irradiation of the cerebral hemispheres of the frog inhibits reflex movements. The color of the batrachian integument appeared much darker when the frogs returned to their moist element after being irradiated. After prolonged irradiation frogs, mice, guinea-pigs, rabbits, and birds died, mostly with paralytic symptoms.

That the Roentgen rays exert a powerful influence upon the action of the skin, upon metabolism, and the temperature of the blood, has been demonstrated by Lecercle. In one of my experiments made on dogs alopecia of the area which was irradiated intensely for three hours developed as early as the fifth day. The hair bulbs showed no atrophy, but the epidermis and the skin follicles were destroyed. Microscopical examination of an excised piece of integument showed the usual signs of inflammation.

FIG. 28.—Excoriation in Roentgen-ray Dermatitis (early stage).

Of the experiments on mice the writer is making at the present time it may be reported that depilation began on the fifth day on an average, when irradiation was done three hours a day. The first symptoms showed at thefo rehead. During the time of observation the animals exhibited no disturbing symptoms—only one among

nine died after being exposed to the Roentgen light for twenty-three hours. This mouse was irradiated one-half hour daily for one week, one hour daily for a second week, and two hours daily for the third week. Depilation took place over the dorsum then. Soft tubes had been used for this case exclusively. The autopsy showed slight congestion of the viscera. Microscopical examination revealed the general signs of inflammatory changes. In two of the animals which were treated in the same manner, but in which high-vacuum tubes were used, the integumental changes were slight, but the viscera, especially the intestines, were much more hyperæmic. This would be in favor of the assumption that the soft tubes affect the integument more intensely than the viscera, while the hard ones affect the skin to a slight degree only, but by their greater power of penetration still exert their effects on the viscera.

So much for observed facts. The question how these inflammatory processes are originated cannot be easily answered, because it touches not only physics and chemistry, but has also physiological, pathological, and even bacteriological features. It seems, however, that it can best be answered on the basis of clinical observation. While experiment on the lower animals is extremely useful for comparison, thereby suggesting new ways for investigation on the human body, it cannot be conclusive for the pathology of man. The thick hairy coat of the animal reacts to burns in a way different from that of the human integument. The same must be considered in connection with the effects of the Roentgen rays upon the skin. It will therefore be more proper to compare our knowledge of the conditions produced by ordinary burns of the human skin with those caused by the Roentgen rays. In both a disturbance of nutrition in the walls of the blood-vessels and its consequences become at once apparent. By considering, for instance, the consequences of a simple burn of the second degree it will be found that the destruction of the red blood corpuscles, described by Fraenkel, Lesser, Pavlovsky, Ponfick, and Wertheim, is of no significance even in extensive burns of this kind. According to Hoppe-Seyler even in fatal burns of the second degree the maximum of the destroyed blood corpuscles did not amount to more than 2.4 per cent. The products of tissue change, resulting from the pathological disintegration of the tissues, are much more detrimental. They originate, according to Fraenkel, in the same manner as they do in the digestion of albumin. The albumin is split, absorbs water, and is finally transformed into albumose and peptones. Krehl and Mathews examined these disintegration products of albumin within the human body. From the results of their investigations we may conclude that in burns of the second degree there is, besides destruction of the red blood corpuscles, disintegration of albumin. The consequence of this latter and most im-

portant change is the formation of exudates, which produce albumoses during the process of absorption. And albumose, not being a product fit for assimilation, is eliminated from the organism by the way of the kidneys.

The greater or lesser severity of the clinical symtoms seems to be dependent upon the various degrees of toxicity of these substances. In this way also is explained the fatal outcome of extensive burns of the second degree. In addition, the large loss of fluid (blood plasma) must be considered, which is also the larger the more widely the burned surface extends. The waste of fluid causes a loss of the natural resistance in the organism, so that these toxic products find a much more favorable soil.

In burns of the second degree the destruction of the red blood corpuscles is of much greater importance, since the elimination of a large quantity of them has effects similar to those of carbonic-acid poisoning. To this is added the result of absorption of the products of the disintegrated tissue (toxæmia).

The difference between an ordinary burn and the changes of tissue caused by Roentgen light consists in the slow development of the process. The peculiar chemical influence of the Roentgen light on the tissues is exerted in such a manner that the nutrition of the cells is impaired. It is only when this impairment has reached a greater degree that the signs described above manifest themselves. And these signs are again influenced by the strength and amount of the Roentgen light. A greater or lesser degree of predisposition is also of significance. Effluvium capillorum is explained by inflammatory processes in the matrix cells.

The treatment of the inflammation caused by the Roentgen light is virtually the same as that of ordinary burns. In simple dermatosis (burn of the first degree) applications of Burow's solution are most comfortable for the patient. For the bullous form (second degree) a xeroform-gauze dressing, after the blisters are opened and removed, is indicated for the first few days. Later on is recommended a dressing of a ten-per-cent. xeroform-lanolin ointment which is changed daily, provided there is but scant secretion. The necrotic form (third degree) requires speedy removal of the mortified tissues, the after-treatment being conducted on the ordinary principles of wound treatment, xeroform or iodoform gauze being used, the latter being preferred if there is much secretion. Torpid granulations are stimulated by an eight-per-cent. solution of chloride of zinc.

Therapeutic Indications.—From a study of these pathological considerations we may derive indications for the therapeutic utilization of the rays, just as conclusions are drawn from the study of the deleterious properties of poisons upon which to establish their therapeutic

indications. The most obvious therapeutic application was that for hypertrichosis. In fact, irradiation has become the treatment *par excellence* for large hairy surfaces. It is only for small areas that the galvanocautery or electrolysis should still be recommended.

Since the cure of sycosis is mainly dependent upon most thorough depilation, the beneficial influence of the rays can be well appreciated in this obstinate disease. Favus, eczema, psoriasis, rosacea, acne vulgaris, and prurigo are also amenable to treatment with Roentgen light. Kümmel succeeded as early as 1897 in curing lupus by the rays. He was soon followed by Albers, Schoenberg, Hahn, Schiff, Freund, Ziemssen, Muehsam, Holland, Schenkle, Jutassy, and Neisser. In all their cases at first an inflammatory reaction was observed, which was followed by the drying up of the nodules. The cicatrization of the lupous portion, which has been changed into a fresh granulating surface, took a considerable length of time.

The author has previously reported on his cases of lupus treated by the *x*-ray, and he may add here that the cure of the first patient treated has remained permanent during four years.

The nodules are usually shelled out together with the destroyed tissue. In their place a light red ulcer remains which bleeds on the slightest touch. In one case the nodules shrank and showed a terra-cotta like appearance. Cases of lupus vulgaris have been cured under the administration of moderate energies after a small number of exposures, which did not last longer than five minutes. It is natural that under such circumstances the macroscopical evidence of inflammation does not show itself. Such cases also show very little scar formation, a factor which is not to be underestimated when the face, for instance, is concerned.

In lupus erythematodes irradiation must be continued for a greater length of time than in the cases of lupus vulgaris.

In the case of a woman of twenty-five years, who was irradiated fifteen times (at intervals of two days on an average of twenty-five minutes each time) until reaction occurred, it was not until the twentieth exposure that the redness decreased and some of the nodules began to shrink. After the twenty-fifth exposure the ulceration cicatrized, the scabs disappeared, and no nodules could be found. The redness persisted for six weeks. It was treated with unguentum zinci salicylicum. The cure was perfect.

Successful treatment of nævus vasculosus is also reported.

The curative influence of the Roentgen rays on carcinomatous tissue can no longer be doubted. Pusey, Williams, Weigel, and others besides the author have reported cures in epithelioma. All integumental forms of carcinoma are accessible to Roentgenotherapy, also cancer of the tongue and the cervix uteri at an early stage, but in spite of

this fact it would be extremely unwise to leave to the rays what can be done much more quickly and effectively with the scalpel.

But irradiation should be considered in the after-treatment as well as in inoperable cases. Even after a thorough operation carcinoma cells are often left in the deeper strata which cannot be reached by the knife, but the rays have an influence on these. If the cells can really be destroyed, as future experiments have to prove, a great advance in the treatment of this terrible disease will have been made. The author has up to the present treated four cases of recurrent carcinoma mammæ, in all of which decided improvement can be observed. In a case of adenocarcinoma, recurring three months after most extensive removal by an excellent surgeon, a large infiltrated mass, reaching from the sternum to the axilla, formed within another three months. The supraclavicular region, the shoulder, and the whole upper extremity of that side were markedly œdematous. Near the sternum was a small ulcerating area. The patient suffered temporary pain of great intensity. The writer did not believe that there was a possible chance even of improvement, but the husband urged him to try irradiation nevertheless. The whole area was exposed, first at intervals of some days and subsequently every day, for an average of twenty minutes. There have been sixteen exposures altogether up to the time of writing. After the fourteenth exposure the infiltrated area began to shrink and the œdema disappeared entirely. The recurring growth had reached the pleura, as is evident from the presence of a pleuritic effusion which was aspirated. A specimen taken from the irradiated area showed colloid degeneration, the adenoid character having disappeared. This seems to some extent to show the mode of cell metamorphosis which the cells undergo after irradiation. Microscopical examination revealed adenocarcinoma with beginning colloid degeneration. The tumor showed a resemblance to glandular structure, in most parts the alveoli were completely filled with epithelial cells, so that in some places they appeared like alveolar carcinoma. Some areas had undergone degeneration; their epithelial cells, in size and the degenerated area, except the nuclei, appeared coarsely granular. Changes of the same nature were observed in the epithelium of the skin covering the tumor (also due to the action of the rays). In some parts of the necrotic area a large amount of dense connective tissue and marked vascularity are noted. The leucocytes were increased in number. The patient is at the present time free from pain and her appetite has increased. A few days ago the superficial layers around the ulcerating area shed themselves as scabs. While a fatal outcome will hardly be averted, the powerful influence of the rays in this desperate case has appeared most clearly.

In cases such as this hard tubes must be chosen, while in neoplasms

confined to the skin, soft tubes are preferable. The writer's observation has suggested that irradiation should be begun as soon as union is perfect after the removal of a neoplasm, and should be kept up for a period of several weeks.

As to the technique of Roentgenotherapy it is advisable to expose five minutes first, and after a week, about ten minutes. If, after a third exposure, two weeks after the first, no reaction has occurred, we may conclude that the patient possesses no idiosyncrasy; and he may then be irradiated every second or third day, and finally daily until intense reaction declares itself.

During the tentatory exposures the distance of the tube should be four inches, later on it may be one-half inch only. Some patients like the direct contact with the tube, and the author has seen no harm from it in resistant individuals.

A shield of lead must be fastened over the area surrounding that to be irradiated. It may be attached by a bandage. To the uneven surface of the margin tinfoil or a piece of cork may be added. In the treatment of neoplasms, however, the use of a shield is improper, since it is intended to have the influence of the rays extend as far as possible. During the intervals xeroform salve (1 to 10 lanolin) should be employed.

As first shown by the author (*Münchener medicinische Wochenschrift*, May 6th, 1901, also *New York Medical Journal*, November 16th, 1901) the effect of the rays is also well marked in integumental sarcoma. In a case of melanosarcoma a local cure was effected, although the patient died later on from metastasis. There is no doubt that the course proved the efficiency of the rays on the integument, and if the patient could have been subjected to earlier treatment, a local cure would probably have been effected before metastasis had taken place. Microscopical examination of the growth showed well-developed large sarcoma cells. The pigment was chiefly seen in the form of streaks, but by higher magnification would be recognized as fine granules contained in cells in the connective-tissue framework of the tumor. In some places they resembled netting. Few cells in the alveoli of the sarcoma were pigmented. But some portions of the section, especially the necrotic areas, showed a great amount of pigment. One of the specimens was colored with hæmatoxylin and eosin, a second with Van Gieson's fluid.

That the Roentgen rays possess bactericidal properties cannot be doubted any longer. The antibacterial effect of sunlight is an illustrative analogy. "Where the sunlight has not access, the physician will soon appear" is an old and significant Italian proverb. In harmony with this consideration, derived from the observation of the development of tuberculosis, is the fact that cultures of the tubercle

bacillus die after exposure to sunlight for three hours. When we consider the great similarity between the effect of sunlight and that of the Roentgen rays, the bactericidal property of the latter is obvious. And in fact the staphylococcus, the bacillus coli communis, and the cholera vibrio die after being irradiated for one hour only. That tuberculosis is influenced by the rays can be assumed, the influence being of a bactericidal as well as of an inflammatory character. It is well to remember in this connection that in tuberculosis not only the bacillus but also that product of metamorphosis, which we know as the tuberculous nodule, is to be considered. Artificial hyperæmia, as has been shown by Rokitansky, may also arrest the development of tuberculosis. It is well worth while to investigate this most important question more closely.

It seems, furthermore, that various microbial types show various reactions in proportion to the different qualities of their plasma. Schaudinn (*Pflueger's Archiv für die gesammte Physiologie*, Bd. 77) for instance found that among the protozoa, Labyrinthula dacryocystis Cientk showed no changes at all. The plasma of these types is viscid and inert. It is indifferent to all kinds of irritation, while the lively Amœba princeps (Ehrbg.), the liquid plasma of which contains large quantities of water, shows considerable change, and dies after being irradiated for ten hours. All kinds of infusoria perish after being irradiated for six hours. Thus we may feel justified in expecting from future experiments valuable hints for the rational therapy of microbial diseases.

For the treatment of the face masks made of lead are very handy. During the intervals xeroform salve should be employed by way of prophylaxis.

The patient to whom treatment by the Roentgen rays is advised must be informed of the risks of burning.

DISEASES OF
THE KIDNEYS (SURGICAL), OF THE URETERS, AND OF THE BLADDER.

BY

REGINALD HARRISON,

LONDON.

THE KIDNEYS.

Wounds of the Kidney.—Since the publication of the last edition of this work but little has been added of interest to the literature of this subject. The lines of treatment for open wounds involving the kidney are generally recognized to lie in the direction of freely opening up the tissues and exposing the damaged organ. The question which then arises is the necessity for nephrectomy as opposed to the possibility of conservative measures proving successful. In those cases in which the injuries are very extensive, there can be no question as to the advisability of removing the kidney at once. But when only a small portion has been crushed or torn, it may sometimes be feasible to remove the injured part and leave a considerable amount of healthy kidney behind. It is only when the crushing or laceration affects the upper pole of the kidney that such a procedure can be contemplated, for when the destructive effects of the lesion involve the lower and middle portions the pelvis and ureter almost invariably suffer.

In limited injuries of this nature the portion of kidney to be removed will sometimes be found already separated, at other times connected to the kidney only by a small bridle of tissue. Hemorrhage has usually not been severe, and the portion involved having been removed by knife or scissors, the wound in the kidney should be closed by deeply placed sutures of carefully sterilized catgut. The kidney tissue in some cases, especially in those in which some little time has elapsed between the injury and operation, is extremely friable. The stitches may be applied somewhat after the manner of Halsted's mattress sutures, these being less liable to cut through the softened tissue. Max Brödel [1] advises three lines of suture for the kidney wound. The first

of fine catgut is placed between the calices, including the fat and fibrous tissues, without involving the mucous surfaces. The second consists of a series of mattress sutures, three or four in number, according to the length of the wound, which bring together the cortical incision, and lastly a continuous suture of fine catgut closing the fibrous capsule.

The effects of wounds of the kidney made for surgical purposes throw some light upon the advantages to be gained by conservative measures of the character described above. Not seldom has it been found that a wound made through the cortex of a kidney for the purpose of exploring for stone has resulted in the atrophy of the organ to such an extent that it has been rendered useless. This was well exemplified in the case of a man upon whom I operated in 1896.

H. P., aged 52 years, was admitted to St. Peter's Hospital for supposed renal stone. The right kidney was cut down upon and exposed. It was large and congested to the eye, while to the finger it felt extremely tense and elastic. It was carefully palpated and the pelvis and commencement of the ureter were also examined. No stone being felt the pelvis was opened by an incision about two inches in length through the cortex, and carefully explored with the finger. A flexible catheter was passed from the pelvis to the bladder the whole length of the ureter, but no resistance was encountered. The cortical wound was therefore closed by three catgut sutures, and the kidney, which had been partially delivered upon the loin for the purpose of this examination, was replaced. The after-history of the case for some weeks was uneventful, and the wound closed satisfactorily.

Shortly after the patient had been allowed to walk some pain was again felt in the right loin. This steadily increased until four months later it was so unbearable that the patient asked for removal of the kidney. I cut down upon it in the line of the old incision, but found only a small, shrivelled mass representing the large and tense kidney of four months previously. Nothing further was done, the wound healed satisfactorily, and the pain very slowly subsided. At the time of writing this patient is perfectly well. In this case then a large tense kidney within six months atrophied and became useless following a small incision for exploratory purposes.

My colleage, Mr. P. J. Freyer, has reported to me recently a case in which he removed a small kidney weighing only a few drachms, the atrophy in this case following an exploratory operation performed by another surgeon, at which nothing abnormal was discovered, but the cortex of the kidney was very freely opened.

In this connection mention must be made of an interesting paper [2a] by Howard A. Kelly, in which by the aid of very clear illustrations he demonstrates the best line which incisions into the kidney cortex should follow to inflict as little damage as may be upon the renal pyramids and the blood-vessels.

It seems to be indisputable, however, that a fairly limited wound

inflicted with due care, as in the cases I have quoted, may be followed by great atrophy of the organ, and it is at least open to question whether the same result would not follow the accidental infliction of an equally severe injury when conservative methods have been adopted.

In the case of punctured wounds and those inflicted by modern high-velocity rifle bullets experience has shown that when the hemorrhage is slight they may safely be left alone.

In the recent South African war bullet tracks involving the kidney were of very frequent occurrence. According to Mr. Makins' they healed rapidly when uncomplicated, and were probably of no more importance than ordinary exploratory punctures surgically inflicted. This author says: "The common history of the symptoms after a wound of the kidney was moderate hemorrhage from the organ, persisting for two to four days. In one of the cases related this hæmaturia was accompanied by the passage of ureteral clots, but this was not a common occurrence." Indeed, upon looking over the cases quoted we find that the men returned to duty at the end of three or four weeks, apparently none the worse for the experience, always supposing that the case was not complicated by any other injury.

Severe wounds of the kidney, in which the abdominal cavity is also involved, present usually, in addition to the symptoms more strictly referable to the kidney, signs of intra-abdominal hemorrhage. In such cases a laparotomy is usually indicated, for though there may be no doubt that hemorrhage from the kidney is taking place, there is also the possibility of hemorrhage from some other abdominal organ to be considered. The prognosis in these cases is usually extremely bad, first, because as a rule an injury sufficiently severe to cause serious intra-abdominal hemorrhage from the kidney will cause other and perhaps more serious injury to other organs, and secondly, because the shock of these injuries is so great that the added shock of an operation of the magnitude generally necessary is ill supported by the patient. The employment of copious saline infusion into a vein coincident with the operation, and provided the hemorrhage can be stopped, is of value.

Movable Kidney.—It is asserted that the kidney is attached sometimes to the posterior abdominal wall by a true mesonephros or peritoneal ligament, which when unduly long permits of too great movement on the part of the organ. In a fairly extensive experience I cannot say that I have ever met with a case in which this condition, to which the term floating kidney has been applied, was demonstrably present. In all cases of movable kidney the pedicle, consisting of blood-vessels, nerves, and areolar tissue, is of necessity long, and it is this fact which has probably led to the description of true floating kidneys. Movable kidneys may be present as a part of a general loose-

ness of the abdominal viscera, to which the term Glénard's[1] disease has been applied, or they may be the only organs affected.

In discussing the etiology of the condition many theories have been suggested. The greater frequency of the condition in women, and especially multiparous women, has led to the belief that the altered conditions of abdominal tension and the sudden and great relaxation dependent upon pregnancy and parturition are largely causative factors in the production of this distressing condition. Considerations of space prevent discussion of this and other theories, but mention must be made of a fact which may have a bearing upon the causation of movable kidney, and which certainly has great importance in the question of treatment.

Others besides myself have remarked upon the great increase in the amount of perirenal fat which is present in a large proportion of cases operated upon. This increase is not merely a participation in a general deposit of fat all over the body, for it is frequently noticed in the cases of floating kidney occurring in individuals of a spare habit. The kidney lies normally in a capsule composed of areolar tissue largely filled with fat; in the cases referred to this capsule is very much larger and looser than usual and the fat is greatly in excess of the normal.

In the treatment of the slighter forms of undue mobility a well-fitting abdominal belt usually proves sufficient, but when this is inadequate to the relief of the pain and uneasiness, operative measures must be resorted to. Very many different methods have been advised and all have given some good results in the hands of those originating them, though it must be confessed that many recurrences after operation have also to be recorded. I shall not describe all the operative measures which have been proposed in the past six or seven years to which the terms nephropexy or nephrorrhaphy might be applied, but only a few of the more striking ones.

Vulliet's Operation.[2a]—On the assumption that recurrences after operation are in many cases due either to the cutting action exerted upon the tissues by silk, silkworm gut, and other slowly absorbed sutures, or to the too rapid absorption of material such as catgut, Vulliet, of Geneva, devised this operation which bears his name.

In the first place the kidney is exposed from the loin in the usual way, and all excess of fat is cleared from the capsule. An incision is then made in the back, about two inches outside the spines of the vertebræ, and a tendon of the longissimus dorsi sought for. This is freed at its lower end and passed through the muscles of the back so as to emerge in the renal fossa anteriorly. The tendon is then carried around the kidney, passing under a small portion of the true fibrous capsule of the organ, or piercing only the fatty capsule, and is brought

again through the muscles of the back. On pulling upon the tendon the kidney will be drawn tightly upon the posterior wall of the abdomen, resting in a kind of sling. The end of the tendon is then sutured into place and both the wounds are closed without drainage.

Another ingenious operation has for its object the adherence of a raw surface on the external aspect of the kidney to a similar surface on the abdominal wall. The kidney having been exposed, a flap of the true capsule, about two inches long and one and one-half inches wide, is raised from its postero-external aspect. Two parallel incisions two inches in length and about one inch apart are then made upon the anterior aspect of the quadratus lumborum muscle and the surface between the two incisions is well freshened with knife and forceps. The flap of capsule is pulled through the two incisions and tightly stitched in place, the raw surface on the kidney whence the flap was raised being brought into apposition with the raw surface on the quadratus.

The only criticism to be offered on these and many other elaborate methods is that they are totally uncalled for. In the large majority of cases no stitches are needed through the kidney substance, no flaps need be raised from the kidney capsule. If the fat is carefully cleared from the fatty capsule and the latter is dragged upon, it will be seen that the kidney is lying in a very loose bag, formed of a fine fascial envelopment enclosing the fat. This should be reduced by careful cutting with scissors or knife until sufficient envelope is left firmly to grasp the kidney. It should then be closed with fine silk sutures, and, the sutures being brought through the muscles severed by the usual oblique lumbar incision, on being tightly tied drag the kidney in its now close-fitting capsule against the abdominal wall, and at the same time serve as buried sutures, closing the severed muscles. No further freshening is required, the free clearance of fat causing quite sufficient development of scar tissue to keep the kidney in its place.

Renal Calculus.—The diagnosis of stone in the kidney has been much improved within the past few years by the use of the *x*-rays. Jonathan Hutchinson, Jr., states[4] that "the skilled use of the Roentgen rays will now rarely fail to demonstrate both the exact position and the size of any renal stone"; and again, "by varying the time of exposures to the rays any calculus can be detected in an ordinary patient." These two statements form a very striking claim for the method of diagnosis referred to. In the writer's own experience cases have occurred in which no shadow was observable with the rays and yet a stone was found; and, on the other hand, in which apparently the shadow was undeniable and yet no stone was discovered by operation.

Mr. Henry Morris repeats[5] in the recent edition of his "Surgery of the Kidney and Ureters" the statement which he made in his "Hunterian Lecture on Renal Surgery." His later utterance is as

follows: "The *x*-rays have now been repeatedly employed in cases of suspected calculus; and in some cases with admirable effect. But the results are most unreliable; shadows having been found when no calculus was present, and no shadow obtained when a calculus existed; and were the negative results allowed to influence surgical treatment, many patients who are now cured by operation would be left to linger on in suffering till they die."

Howard Kelly, on the other hand, speaks with no uncertain voice in favor of the *x*-rays: "The diagnosis of stone in the kidney has fortunately been so greatly simplified by the use of the *x*-rays that with this agent we can now determine the presence or absence of stone in all cases with practical certainty."[6]

How are we to reconcile these very divergent opinions? Hutchinson states that the permeability of calculi by the rays varies with their composition, and probably in this fact lies the explanation of the very varying results which have been obtained. It is interesting to note that almost all the cases described by him in the paper quoted above were those of patients suffering from oxalate calculi, which all observers agree are the most resistant to the rays. Still he distinctly states that shadows can be obtained with any calculi, the effect depending upon the length of exposure to the rays.

The truth lies, as usual, most probably between the two extremes. A well-marked shadow would encourage operation, but the absence of one, other symptoms being present, should most certainly not deter the surgeon from an exploratory nephrotomy.

Renal Tuberculosis.—Partial removal of a kidney infected with tubercle has been recommended more than once in the past few years, but conservative surgery in this instance is not advisable. The only case in which a portion of a tuberculous kidney could be removed with any hope of success is one in which a single caseous deposit or small localized abscess exists in one or other pole of the kidney. Such conditions are excessively rare and are almost if not quite impossible to ascertain with certainty before the kidney is removed from the body. Far commoner is it to find either a generally scattered deposit of tubercle through the kidney substance or several caseous deposits fairly widely separated from one another. The removal of a half or even a quarter of the kidney gives us no assurance that early deposits are not present in the portion left behind, impossible to recognize by touch, and equally impossible to recognize by sight unless the kidney is positively sliced in several directions.

In this connection, however, it is only fair to quote cases in which the opposite view has been held and in which success justified the operation. A striking instance is that brought forward by Henry Morris.[7] A woman had suffered removal of one kidney for tubercu-

losis in Canada, and Mr. Morris excised about one-third of the remaining kidney. This patient was still alive and in active domestic service four years after this partial nephrectomy.

This author quotes seven partial nephrectomies occurring in his own practice. In three of these total nephrectomy had subsequently to follow. The remaining four, of which the case quoted above was one, were known to be alive two and a half years to four and a half years after operation. But Henry Morris does not discuss the question that has been raised here, viz., the extreme difficulty of deciding how much of the kidney is diseased and how much it is safe to leave behind. In considering any question of operation upon a kidney suspected to be tuberculous, the most pertinent point that arises is necessarily the condition of the opposite kidney. If the second kidney is much diseased it is obviously unjustifiable to remove either, for the result would simply be to shorten life. Hence it is of extreme importance to ascertain the condition of both kidneys before committing one's self to the removal of one. The ordinary methods of palpation may be employed, but in many instances they give little or no assistance, for a very considerably diseased kidney may be placed somewhat high under the protection of the lower ribs and hence may not come within reach of the examining hand, while a perfectly healthy kidney, somewhat enlarged by reason of the extra work thrown upon it by its diseased fellow, may be placed low down and therefore easily felt, and firm pressure upon it may give rise to sensations of tenderness, such as those experienced on squeezing between one's hands a perfectly healthy but so-called floating kidney. The cystoscope, however, offers some help, and though it is not absolutely to be relied upon for a diagnosis the confirmatory evidence it affords is sometimes of value.

Hurry Fenwick states[8] that in the earliest stage of infection of the bladder from above, the orifice of the ureter has lost its slit-like shape. "It is open, its lips are rounded, the epithelial surface is dull, the area around it is swollen and patched with extravasation. . . . The opposite ureteric orifice is normal."

Supposing the disease to have advanced to a certain degree in the kidney, but not sufficient to affect the ureteral orifice to the extent quoted, ureteral catheterization may sometimes prove serviceable. In females Kelly's method may be used, now familiar to most surgeons from the excellent descriptive articles published both in this work and elsewhere. In the male the special forms of cystoscope, recommended by various authors, are at the surgeon's service. Very considerable practice, manual dexterity, and some patience are indispensable factors in this method of diagnosis. The ureters being catheterized, the urine from each is separately collected and examined, furnishing a valuable index of the condition of either kidney.

The claims made for cystoscopy vary generally with the experience of those who use the method. Hurry Fenwick, who has perhaps done more than any other English surgeon to popularize the instrument in this country, writes as follows: "A patient applies with tubercle in the urine and an easily felt movable kidney, in or around which a slight aching is complained of. Is that kidney to be removed? It is a tempting diagnosis to locate the tubercle in that kidney, and to advise nephrectomy. But in some cases the clinician will be wrong, and the operator will remove the wrong kidney if he acts upon this impulse, for the movable kidney may be the healthy gland.

"Tubercle of the kidney in some cases progresses very quietly, and as the disease gradually cripples the secreting texture, its fellow-gland takes on more and more of the work. With the increased activity it enlarges and very often aches. In women especially, a compensatorily hypertrophied kidney becomes feelable and movable. Cystoscopy will show in this case that the feelable and movable gland is healthy, for it has a normal or slightly enlarged ureteric orifice, while the opposite kidney will be seen to be diseased, for its ureteric orifice has an irregular outline and widely open, thickened mouth; and that it is displaced."

It must not be lost sight of, however, that a kidney may be seriously affected with tubercle without offering any evidence of its condition either from the condition of its ureter or from the quality of the urine excreted by it. A very large caseous nodule in an early stage before any breaking down has occurred will furnish no tubercle bacilli to the urine and will have no effect upon the appearance of the corresponding ureteral orifice, for it is obvious that before any noticeable products of such a nodule can appear in the urine the process of breaking down must have proceeded from the deposit in the cortex through the mucous membrane of the renal pelvis. This point must be remembered when seeking aid from the cystoscopic examination of the bladder in cases suspected of renal tuberculosis. But diagnosis in difficult cases rests not upon any one sign, but upon a collection of evidence, and enough has been said to show the value of the instrument as an adjunct to other clinical methods.

In tuberculosis of the urinary organs Koch's new tuberculin may be used when the disease is recognized sufficiently early. It is useless in the later stages when the disease has spread throughout the urinary system and may even be generally disseminated in other organs. This subject is referred to more fully in the section on ulceration of the bladder.

Renal Syphilis.—Syphilitic affections of the kidney may be divided into two main classes, according to their incidence in acquired or inherited syphilis.

In the secondary stage of acquired syphilis albuminuria may occur with the appearance of the rash. It is usually transient and is not of very great clinical importance when dependent upon syphilis alone. Other causes must be excluded in the diagnosis. I have found it to occur in from three to eight per cent. of secondary syphilides.

The use of mercury has been said to account for albuminuria occurring in secondary syphilis. Probably mercury as now used has no such effect upon the renal cortex. In a series of one hundred and forty cases of syphilis examined early in the secondary stage before any mercury had been administered, John Pardoe noted twelve cases in which albuminuria was present. In five of these cases there was a precedent history of renal trouble, dependent in three of the five upon recent scarlet fever. The albuminuria in all but two of these cases disappeared while under mercurial treatment.

In the later stages of acquired syphilis renal trouble is, though not so common perhaps as in years gone by, not of very great rarity. The changes observed have been of all descriptions—amyloid, interstitial, parenchymatous, and gummatous. The three former varieties do not differ either clinically or pathologically from the same conditions dependent upon other causes. Gummatous disease of the kidney, as stated by Henry Morris, is of interest from the fact that it may be mistaken for malignancy or tuberculosis. He quotes cases observed by himself, Bowlby, and Israel.

In Bowlby's case[1] a swelling was noticed in the right renal region, obviously the kidney. It was hard, freely movable, the urine contained a trace of albumin. A year later the tumor formed a definite renal tumor, hard and movable. There was still albuminuria. There was a history of syphilis twenty-one years previously.

Nephrectomy was advised and performed. The kidney weighed seventeen ounces; all traces of kidney structure had disappeared and all that remained was a mass of gummatous and fibrous tissue.

The treatment of syphilitic disease of the kidneys cannot be laid down on hard-and-fast lines. In the earlier stages thorough treatment by mercury is advisable. The effect of the drug must be most carefully watched and the patient's general health improved by residence at the seaside, combined with liberal diet and the exhibition of such tonics as iron, quinine, and cod-liver oil. When much gummatous degeneration has occurred, as in the case recorded by Bowlby, probably operation is the best course to pursue, provided always that fairly satisfactory evidence as to the healthy condition of the opposite kidney is forthcoming. It is always wise, however, to submit such cases to a thorough and prolonged course of iodide of potassium in large doses, and in those cases in which both kidneys are affected this is indeed the only treatment available. In the case of a single gumma of

the kidney, provided only a portion of the organ is affected, partial nephrectomy would seem to be indicated, and would have a much better chance of success than the same procedure in cases of tubercle. It is probable that a single gumma would be amenable to iodides, but if such a condition is discovered at the time of operation following a course of these drugs given without apparent benefit, I shall have no hesitation in performing this operation.

Angeioma of the Kidney.—Symptomless hæmaturia may occasionally be due to an angeioma of one or more of the renal papillæ.

Hurry Fenwick has recorded a case in which very considerable hæmaturia was the only prominent symptom. On cystoscopy the bleeding was seen to be proceeding from the ureteral orifice. The corresponding kidney was therefore cut down upon and carefully examined. Nothing abnormal being discovered, the pelvis was opened and the edges of the wound held apart while a strong light from an electric brow-mirror was directed into the pelvic cavity. It was then seen that the hemorrhage was proceeding from an apparently varicose enlargement of one of the papillæ. The projecting portion of the papilla was removed, the pelvic wound closed, and the lumbar incision sutured in the usual way. The hemorrhage completely ceased and had not recurred many months after operation.

Renal angeioma more commonly occurs in the parenchyma of the kidney. Morris says that it is usually situated in the medullary substance or immediately beneath the capsule. He quotes[10] the case of one of his patients who suffered from very profuse hæmaturia occurring in definite attacks, each attack lasting from three to four days. She died from septicæmia following acute cellulitis of the leg, and at the post-mortem examination the cause of the hæmaturia was found to be multiple angeiomata of the left kidney, one of which had ulcerated into a calyx. These angeiomata appear to differ from the varicose condition observed by Fenwick, for they were arranged in a plexiform manner chiefly in the medullary substance between the pyramids, and following the course of the vessels.

The only treatment possible in such a condition would be a nephrectomy, and here again the condition of the opposite kidney must be a source of grave conjecture. If no signs of enlargement of the opposite kidney, and no hemorrhage from it could be detected, it would be justifiable to operate.

Renal Tension and its Treatment by Surgical Means.—In 1896 I drew attention[11] to some cases in which patients suffering from albuminuria and other renal symptoms, which might have been produced by a stone, had completely recovered after an exploratory operation on the kidney, though no calculus was discovered. Since the publication of that paper a considerable number of contributions to the subject have

been made by both British and foreign authors. In a communication [12] under the title given above, made to the surgical section of the *British Medical Association* in July, 1901, I reviewed some of the observations which had been made during the preceding five years and drew the following deductions: That the satisfactory results in these cases might be ascribed to the relief of tension and congestion, thus allowing the escape of that which caused these conditions, and permitting the return of a natural circulation in the organ.

Describing the condition of the kidneys in some acute attacks of nephritis the following passage appears very striking and suggestive: "Sometimes, particularly when the attack is the result of a definite exposure to cold and the subject middle-aged and intemperate, an acute form of nephritis manifests itself, which is characterized by extravagant congestion, even to chocolate or purple, and great and rapid swelling of the gland; so that, as I have seen at least in one instance, the kidneys have burst their capsules. Short of this exceptional result the whole organ, but chiefly the cortical tissue, is enormously swollen, the cortex changed to a deep coffee color and the cones to purple, while the tubes are distended with epithelium and blood." [13]

In such a case as this death is the inevitable result, and in congestion of a somewhat less degree than that here described it is difficult to understand how repair can be carried to a successful issue without some mechanical assistance.

The question has been raised, How is it that the tension of acute nephritis never or rarely proceeds to suppuration or gangrene, as happens elsewhere in the body? The answer is obvious. These extremes are anticipated by death.

Certain analogies exist in other regions of the body where the effects of high tension produce similar destructive results. Perhaps the most striking of these is glaucoma which, if unrelieved by surgical means, very surely destroys the eye, at all events for visual purposes. The similarity of the two conditions is so striking that the term renal glaucoma has been suggested as descriptive of the congested condition of some kidney lesions.

Again in the testicle, when it becomes inflamed, we have not infrequently permanent evidence of the damage which unrelieved inflammation and tension are capable of inflicting on an organ which, relative to its secreting and investing structures, is not unlike the kidney. The late Mr. Henry Smith pointed out the value of puncture or incision through the capsule in acute forms of orchitis. It was correctly asserted that not only was the pain of tension in a highly sensitive organ relieved, but structural damage averted. In fact, sterility was by this simple means rendered unlikely to occur.

The question that naturally arises is in what class of cases should

operative measures be resorted to? They seem to me to fall under two headings, first, cases of a somewhat chronic nature, when after a more or less acute attack of nephritis the kidneys return to a better condition but do not wholly recover; and secondly, cases extremely acute in their course, where death rapidly ends the scene unless the surgeon can step in with aid.

It may be objected that most of these conditions are bilateral, and that an operation will therefore of necessity be required on both kidneys; but many of the patients to whom I have referred complain only of suffering upon one side, those in whom the suspicion of renal stone has led to operation, a suspicion unverified when an operation has been performed, but in which nevertheless the patients are cured. In the acute cases I would meet the same objection by saying that if the tension is so much relieved upon the one side as to allow the kidney to do double the work it was capable of when so hampered, a considerable strain must be removed from the other kidney; and further in such desperate cases so simple an operation in its nature as the puncture or limited capsular incision which I recommend, can be performed, without greatly increasing the risk, even upon both kidneys.

The operation in itself is of extreme simplicity. The kidney is cut down upon from the loin by a very moderate incision, the fatty capsule opened, and the organ carefully identified. An incision of from one to three inches is made through the true capsule along the convexity of the kidney. If great congestion is present the incision may extend with advantage into the cortex. A drainage tube is placed in the wound reaching to the kidney surface, and the wound is closed around it. In a spare subject such an operation as this occupies but ten or fifteen minutes.

The subject is on its trial, but I believe that further experience will serve to indicate the cases in which it is of value and will confirm the opinions here expressed.

THE URETERS.

In the course of the last six or seven years considerable material has accumulated from observations upon disease and injury of the ureters. Mention must first be made of catheterization of the male ureters, a subject which was scarcely sufficiently advanced at the time of the last issue of this work to merit more than passing recognition.

This operation necessarily must be carried out under internal illumination of the bladder, and it is to the labors of Nitze, Casper, and Albarran that we are chiefly indebted for practical methods of working. I shall not describe the various instruments at present in

the hands of surgeons, but will merely say that the most practical instrument for the purpose at present is that of Albarran.

A perfectly clear medium having been obtained, either by directing the patient to hold urine for some hours when this is possible and the urine is clear, or by careful irrigation when the urine is cloudy, the catheter-cystoscope is passed and the ureteral orifice sought for. The tip of the ureteral catheter is made to protrude, and guided by the eye is engaged in the opening. Steady pressure is maintained and the catheter is seen to pass obliquely through the wall of the bladder and can then be inserted as far as is wished, provided no obstruction in the ureter is present. The cystoscope is then withdrawn, armed with another catheter and reintroduced. The same procedure is undertaken, and the cystoscope being finally withdrawn, the two catheters are left *in situ*, their ends being placed in separate tubes for the purpose of collecting the urine from each kidney separately. The operation is a very delicate one, requiring considerable skill and experience on the part of the operator, while in certain cases it is rendered practically impossible by the condition of the bladder.

Such conditions are the following: Great enlargement of the prostate on its vesical aspect. In this condition the necessary manipulations are much impeded by the obstructing growth. The relations of the ureteral orifices to the internal meatus urinarius may be so altered that the orifices are difficult to find, and when found are often at an impossible angle to negotiate with the ureteral catheter.

Trabeculation with sacculation and pouching of the bladder walls renders a search for the ureters practically hopeless sometimes. The approximate position of the orifice may be detected by noting the little swirl or eddy which takes place on the discharge of urine into the bladder, but the opening may be placed immediately behind a ridge or at the bottom of a depression, in either situation impossible of access.

In conditions such as tuberculous infiltration of the bladder base, and in some other inflammatory conditions there is great intolerance of any vesical distention. Sufficient distention is a necessary postulate for success in ureteral catheterism, but in some cases the bladder will not contain more than two to three ounces of liquid.

The presence of large calculi in the bladder, of vesical growths springing from the neighborhood of the ureteral openings, or of hemorrhage from either ureter obscuring the view, renders this operation equally impossible in such instances.

But when the bladder is practically healthy, the medium clear, and the capacity sufficient, an operator who is well grounded in the routine use of the instrument should not find any great difficulty in the performance of ureteral catheterism.

Several objects are gained by the successful practice of this method,

In females a catheter inserted into each ureter forms a valuable guide to the position of these ducts, in cases of hysterectomy when the ureters run a chance of being wounded during the operation.

In either sex the determination of the character of urine secreted by each kidney forms a reliable indication of the condition of these organs. Stones impacted in the ureters may occasionally be detected, or at the least it can be definitely asserted that an obstruction exists at a certain spot.

The value of ureteral catheterism in connection with the operation of nephrectomy has already been discussed. It is only by considerable experience, however, that sufficient skill can be attained to give the operator reliable results.

Ureterotomy, Ureterectomy, and Ureteral Anastomosis.—The operation of ureterotomy consists in opening the ureter for the purpose of exploration or to remove a calculus. In the male the whole length of the ureter can be explored from an incision which, commencing somewhat like Abernethy's incision for tying the external iliac artery, can be continued upward to the loin and downward to Poupart's ligament. The peritoneum being pushed inward, a good view of the ureter is gained. In the female the upper part of the ureter can be examined in the same manner, but a stone impacted in the lower third can be more easily removed by an incision through the vaginal roof. In either case the wound does not require sutures unless the ureter has been divided. The insertion of a tube down to the wound, followed by the use of a gauze drain, usually results in closure of the fistula, unless the damage to the ureter has been so marked as to cause cicatricial contraction so impeding the passage of urine that a permanent fistula forms.

Ureterectomy is necessary for tuberculous ureteritis, and for malignant growths involving the ureter. It may occasionally be called for in cases in which severe injury to the ureter has been followed by so much cicatricial stenosis that the obstruction has been complete; a considerable portion of ureter must be excised before an anastomosis can be performed.

Uretero-pelvic anastomosis and uretero-ureteral anastomosis are operations performed either for restoring the continuity of the duct or for the purpose of improving its relations to the pelvis.

The former operation is called for when the upper portion of the ureter has been much injured in the performance of an operation, such as the extraction of a large stone from the renal pelvis; to restore the connection between pelvis and ureter after removal of a portion of the latter which has become kinked; or to implant the renal end of the ureter in a better position upon the pelvis when some abnormal relation of the one to the other is proved to be the cause of a serious hydronephrosis.

Ureteral anastomosis is used to restore the lumen of the duct after accidental division, after removal of a portion for stricture or for sloughing caused by the impaction of a ureteral calculus, and for rupture due to injuries, whether the rupture is intra- or extraperitoneal.

The methods used for performing uretero-ureteral anastomosis are numerous. They fall naturally under four headings. First, the end-to-end anastomosis in which the divided ends are simply brought together by fine sutures of catgut or silk. Several successful cases have been recorded, but objections to the method are that perfect union is very doubtful, considerable leakage tending to take place. The more leakage that occurs the greater is the tendency to stenosis, and the circular character of the anastomosis also predisposes to this.

The end-in-end method of Pozzi [14] consists in dilating the inferior cut extremity of the ureter and invaginating the upper extremity into it by passing two sutures through the upper end, threading the two ends of each suture upon separate needles and passing these from within outward through the dilated lower end. These sutures when pulled upon drag the upper into the lower end, and the sutures can then be tied.

The operation of Van Hook, or lateral implantation, was described in the first volume of this work. A slight modification was introduced by Emmet of New York, who sutured the upper segment to the lower all round the incision in the latter.

End-to-end oblique anastomosis, or the method of Bovée,[15] was devised to overcome the objections to the direct end-to-end anastomosis and that of Van Hook. The ends are cut in a slanting direction, and the stitches are put in so as not to penetrate the mucous membrane. To insure accurate adaptation of the ends, one to the other, the author put in alternate mattress and straight sutures. The result in one recorded case was excellent, and the after history showed no signs of commencing stricture some months after operation.

THE BLADDER.

But little work has been undertaken on ulceration of the bladder, or perhaps, to speak more correctly, very few results of purposive work in this direction have been published, although a large number of isolated observations have been recorded. In a recent small work [16] E. Hurry Fenwick has given the results of some ten years' careful study of vesical ulceration, and the conclusions which he draws are extremely interesting, although he is careful to deprecate at present any claim to finality.

In approaching the study of such a subject some method of classification is obviously necessary. The classification suggested by Mr.

Fenwick, although somewhat free, is sufficiently elaborate for the purpose. He divides ulcerations of the bladder into three main groups:

A. Simple ulceration. 1. Spontaneous. 2. Consecutive.

B. Tuberculous ulceration.

C. Malignant ulceration.

Simple spontaneous ulceration of the bladder must be pronounced to be of exceedingly rare occurrence. By spontaneous I indicate that the ulceration is of much the same character as simple ulcer of the stomach, *i.e.*, that so far as we can discover there is no dependence upon some other diseased condition for its production. Fenwick divides ulcers of this nature into two classes, acute and chronic. It must be confessed, as this author is the first to admit, that his recognition of acute spontaneous ulceration of the bladder does not rest on a very secure basis, for he is able to adduce only one case in evidence of his assertion. Such a condition as an acute solitary perforating ulcer of the bladder wall is quite conceivable, but is of such extreme rarity that prolonged consideration of it would be out of place here.

Simple chronic spontaneous ulceration, on the other hand, is a condition of more practical interest. The introduction of the electric cystoscope has rendered accurate observation of intravesical conditions quite attainable by those who care to take the trouble to master the technique of the instrument, and who have sufficient clinical material to work upon. Formerly the recognition and classification of such conditions as these was impossible, for they could not be diagnosed by digital examination through a suprapubic or a perineal wound. Simple chronic solitary ulcers of the bladder must be distinguished from chronic solitary tuberculous ulcers of the bladder, and the diagnosis rests upon somewhat insecure foundations at present. The appearance of the two forms of ulcer is practically identical, the clinical symptoms are almost equally indistinguishable. The diagnosis must therefore rest upon the presence or absence of tuberculous deposits elsewhere, and the detection or absence of tubercle bacilli in the centrifugalized urine.

The ulcer is almost always if not invariably situated upon the bladder base, sometimes a little to the outside of one or other ureteric orifice; according to Fenwick almost without exception to the inner side. Its appearance necessarily varies with the amount of distention of the bladder cavity, and the consequent stretching or relaxation of the bladder walls. With moderate distention the edge of the ulcer usually appears thick and somewhat inverted, the base is covered sometimes with adherent clots, sometimes with shreddy slough upon which phosphates are frequently deposited. If hemorrhage has recently occurred the surface of mucous membrane immediately surrounding the ulcer has a somewhat reddened appearance, probably

due to the staining consequent upon the shrinkage of the soft clot which is frequently adherent to the ulcer. The remainder of the vesical mucous membrane is clear, and shows practically no change even up to the very margin of the ulcer.

The *symptoms* of this condition are three in number, viz., pain, frequency of micturition, and hæmaturia. Taken as a whole the symptoms are characterized by their intermittency. Hæmaturia is very variable. It may be merely a little oozing, barely sufficing to tinge the urine. From such a minimum it may pass to a maximum severity, hemorrhage being profuse, arterial in color and persistency, leading even to agonizing distention of the bladder by clots. Slight causes appear to be sufficient to produce it. Extra exertion, particularly of a character calling into play the abdominal muscles; sudden shock as in leaping from a height and alighting heavily upon hard ground, and retention of urine longer than is comfortable, the latter generally owing to circumstances delaying convenience for the act. The pain too is very variable in its incidence, but when present it is much more constant in its character. Continual fixed pain is sometimes complained of, referred to the upper sacral region, and in many instances just over the front of the pubes also. Pain is complained of at the penoscrotal angle, much intensified on over-retention of urine, equally relieved by the act of micturition. Frequency varies *pari passu* with the other symptoms. It is rare to have frequency of micturition in these cases without pain, and usually when frequency and pain increase, hemorrhage very shortly makes its appearance, but frequency and some pain may exist for considerable periods without hæmaturia. The pain is rarely referred to the glans penis, and is usually relieved by micturition, thus differing from that of calculus.

The *prognosis* when no signs of tubercle are present in these cases of solitary chronic ulcer is decidedly good. The chronicity of the ulcer varies much with the means adopted for its relief.

Treatment in the early stages is usually restricted to the use of bladder washes and instillations and the careful building up of the patient's constitution by residence in a good neighborhood, preferably at the seaside in summer, and some fairly dry equable climate in winter, plenty of nourishing, easily digested food from which all known bladder irritants are excluded, and the exhibition of such drugs as oil of sandal wood, urotropin, cystamin, and the like urinary sedatives and antiseptics. If improvement is not soon marked under such a régime, operative measures must be undertaken. Indeed, Fenwick speaks strongly on the value of early operation in all these cases. "Curettage and excision yield such good results that they should be undertaken as soon as possible. I urge this more especially because of the difficulty of saying whether the solitary ulcer is benign or in-

fected with tuberculosis, and the same treatment is sound surgery for both classes. . . . I know of no curative medicine when once the ulcer has become encrusted with lime phosphates . . . the best way is thoroughly to scrape the surface of the ulcer."[17]

Chronic consecutive ulceration dependent upon many different causes usually heals when the cause is removed. In very long standing cases, however, the bladder does not tend to recover in the way one expects, however carefully irrigations and instillations may be performed. The indication then is for rest, and this cannot be attained except by free drainage of the bladder. For many years I have been in the habit of draining such bladders as these with the happiest results. The method to be employed is that of perineal puncture and drainage with a rigid tube until sufficient time has elapsed for a track to form, followed by the substitution of a soft-rubber perineal tube which may be worn with little or no discomfort and without interference with most ordinary occupations for as long as may be thought necessary.[18], [19]

Tuberculous ulceration of the bladder may sometimes be seen in the form of a solitary ulcer, when the appearances and treatment are much the same as those of the ulcer of a benign character. But more usually infection is of a much more diffuse character. It may be, to all appearance, primary or it may be simply part of a general invasion of the system starting from some other tuberculous focus. The condition usually commences as a submucous deposit of tubercle in minute scattered areas or in somewhat irregular patches. Swelling and minute extravasations occur around these foci, which after a time tend to run together and coalesce. Later ulceration takes place in irregular patches, the ulcers having an irregular margin and a great tendency to undermine the mucosa. Phosphatic débris collects and adheres to these erosions until finally the whole bladder base may be converted into an ulcerated surface covered with patches of encrusted sloughs.

The *treatment* of vesical tuberculosis varies with the stage to which it has progressed. In the earliest stages of a somewhat general infection careful feeding with avoidance of bladder irritants, and the administration of bladder sedatives are indicated. Hurry Fenwick[20] advises the early use of Koch's new tuberculin, commencing with $\frac{1}{10}$ mgm. and continuing with six injections of increasing strength to 1 mgm. He says that "it is surprising, if the disease is recognized early, and treated in this way, how improved the patients are by this means."

Malignant Ulceration.—In the treatment of malignant ulceration of the bladder wall surgery can unfortunately claim to have made but little advance. Operations for the purpose of drainage either by the suprapubic or perineal route give little or no relief. Morphine in incredibly large doses but stills the agony for a very brief period. Pos-

sibly division of the nerve supply to the bladder might give some relief. Mr. Fenwick suggests a very free transverse opening being made suprapubically in the anterior wall of the bladder, to allow the urine to run out into absorbent dressings as fast as it runs in.

Extroversion of the Bladder.—Several methods for the treatment of this most distressing condition have been brought forward recently. The operations for extroversion of the bladder fall into two classes. In the first we have those measures which aim at fashioning a urine-holding bladder from the materials at command by means of plastic surgery. In the second the operator diverts the urine from the raw exposed bladder surface which is allowed to heal over. In the former class no advance worthy of note has been made, and from my experience of such attempts I am inclined to say that however successful surgeons may be in making a bladder, such operations will never be successful in relieving the condition, for I can conceive of no means by which any control over the urine can be restored to the patient.

In the other class of cases more hopeful results have been obtained.

In April, 1897, I showed to the Medical Society of London[1] a youth, fifteen years of age, upon whom I had operated for this condition.

Numerous attempts had been made to close the bladder by plastic operation by various surgeons, entirely without success. On his admission into St. Peter's Hospital in July, 1895, his condition was most miserable. There was a considerable protuberance of the posterior wall of the bladder upon which the orifices of the ureters were distinctly visible. The exposed mucous membrane was very sensitive and bled readily upon being touched by either the hands or the clothes, and the thighs and legs were much excoriated by the constant dripping of urine from above. The boy, then thirteen years of age, was stunted, of very poor mental development, much emaciated, and indeed resembled a child of seven or eight years rather than a boy of thirteen. He unfortunately developed an attack of scarlet fever which necessitated his removal to an infectious hospital. On readmission to St. Peter's in the December following his condition was if possible somewhat worse. After satisfying myself that the kidneys were both working well, and that the urine was healthy, I removed his left kidney by lumbar incision in January, 1896. With the view of allowing ample time for the purpose of enabling the remaining kidney to grow and to provide for the entire urinary secretion, the patient went home for some months, returning occasionally for observation.

He was again admitted to the hospital in November, 1896. His condition was much as before. The solitary right kidney was working well, the urine being well up to normal both in quantity and quality. The right ureter was now transplanted in the following manner: I first passed a flexible bougie up the solitary ureter so as to serve as a guide for finding the duct, as it crossed the brim of the pelvis. I then made a small incision upon the right loin in the same line as for a lumbar colotomy. The ureter was readily found and a carbolized

silk ligature placed upon it just below where it crossed the common iliac artery, and the tube being cut across on the kidney side of the ligature, was brought out into the wound, to the posterior angle of which its open mouth was attached by a fine silk suture. The loin wound was closed, but not so tightly as to press upon the ureter. Before the patient left the operating theatre urine was seen to issue freely from the open mouth of the ureter.

For ten days the after-history was uneventful, but from that time, for five weeks following, a most remarkable series of oscillations in the patient's temperature occurred, varying with great swiftness and irregularity from 97° to 105°. The urine during the whole period remained normal and was freely excreted. On February 27th, nearly three months after operation, the urine was in good condition, specific gravity 1.014, reaction neutral, no albumin, urea 1.3 per cent., no casts or pathological deposit present. From this date until June, 1897, a period of seven months from the date of operation, the boy steadily improved. He grew about three inches in height and there was a corresponding improvement in his mental condition. He was provided with a cup-receiver, which fitted close to the loin and received the urine which then fell into a rubber urinal. His appetite was excellent and he walked well. In the first week of June he was allowed to return to his home, which unfortunately was extremely squalid and miserable, but his parents, who had previously treated him with aversion and cruelty, appeared to take more interest in him now that his condition was so much improved, and desired his return. Three weeks later he returned to the hospital. He had in this interval never once been washed. The urine receiver had never been cleansed, and his condition was pitiable. His skin in the lumbar region was excoriated and raw from the dripping urine and uncleanliness. Pyelitis had set in. Gradually suppuration extended to the kidney substance and he died in July, eight months after the operation, his death being directly attributable to neglect.

In the case I have just described, my object in removing one kidney was to have less trouble in dealing with the escape of urine after transplantation of the ureter. For fifteen years urine had been escaping upon an open raw surface, and it seemed to me that it would make no difference to the kidney if it escaped upon the loin rather than above the pubes. Attempts to direct the ureters into the intestine had proved uniformly fatal from pyelonephritis, but this method seemed to me to hold out more hope of success. So long as the boy was under careful supervision at the hopital his progress was extremely rapid and no untoward result occurred. But when neglected, the pyelonephritis, always feared, made its appearance and quickly ended the scene. The bladder was gradually shrinking, and I proposed to close in the raw surface with skin flaps after dissecting out the small patch of mucous membrane, had not the case terminated so abruptly.

George A. Peters of Toronto has reported a case in which one year and a half after transplantation of the ureters into the rectum the patient was perfectly well, and had considerable control over the urine.

B. S. G——, aged 2 years and 7 months, came under Professor Peters' care in September, 1896, suffering from severe procidentia recti and complete extroversion of the bladder with which was associated, as is usual, imperfect closure of the pelvic arch. A completely successful operation cured the prolapsed rectum, but with this we have no concern. On July 15th, 1899, the operation for transplantation of the ureters was performed.

The sphincter ani was well stretched and the rectum, which had been emptied by a purge and enema, was washed out with an antiseptic solution. A fair-sized sponge with tape attached was passed up the rectum as high as possible. This prevented the passage of fæces and also helped to lift the anterior wall of the rectum toward the bladder. A No. 5 Jacques soft-rubber catheter was now passed for about two inches into each ureter, and a silk suture was "caught" through the extreme end of the ureteral papilla once or twice and also through the substance of the catheter to prevent it slipping out. The distal end of the ureter, including a "rosette" of mucous membrane and bladder muscle, was then dissected free. Both ureters having been freed by dissection along the wall of the pelvis, the whole of the bladder tissue was removed. Great care was taken not to injure the peritoneum. (If a suspicion is entertained that injury to that structure is imminent, the muscle of the bladder wall may be left, but every shred of mucous membrane must be removed.) By pressing back the retrovesical cellular tissue Dr. Peters was able to expose with ease the anterior and lateral walls of the rectum.

The ureters were next implanted in the rectum, above the internal sphincter, in the lateral wall and not anteriorly, so as to avoid kinking, and high enough up to permit the ureter to project slightly. The exact spot having been ascertained, a pair of forceps was passed into the rectum and the points were pressed upon the wall. Upon these forceps the rectum was carefully incised from in front, the opening on either side being just so large as to take the ureter without injuriously pressing upon it. The forceps being opened, the catheter was caught on either side and dragged through, carrying with it the ureter and rosette of bladder tissue already described. Care was taken to see that the ureter projected one-fourth to one-half an inch into the bowel. The raw anterior wound was firmly packed with iodoform gauze and allowed to close by granulation.

One and a half years after this operation the ureters could be felt as salient papillæ as large as the tips of one's little finger in the rectum. There was no eczema or excoriation of the anus or perineum, nor was there any evidence that the rectum resented the presence of urine. The frequency of defecation varied with the amount of fluid ingested and the boy's activity. At night from six to eight hours' rest was obtained; by day the frequency varied from one to three hours. There was no incontinence of urine, or rather of urine and fæces, the boy having very good control over the function.

The great interest of this case lies in several of its features. First, it is an extraperitoneal operation and so differs *in toto* from those proposed by Maydl, Park, Fowler, Halstead, and others. There is there-

fore no danger of peritonitis arising from leakage of either urine or fæcal material.

Secondly, a prominent natural papilla is obtained. As Professor Peters says: "This is the natural manner of debouchement of a duct upon a mucous membrane, and affords the best possible protection against the spread of infection up the ureters."

Thirdly, the ureters are left undisturbed in their natural environment almost to the point of implantation.

And, lastly, the operation is easy of performance and almost free from shock.

There can be no question that this ingenious operation is a distinct advance upon any other method of transplantation that has at present been proposed. Time must be given, however, to see whether the rectum will grow more intolerant or will remain in as satisfactory condition as it was one and a half years after operation. Also more than one case is necessary to assure us that ascending infection, the great drawback to all the other operations proposed, will not occur.

Hernia of the Bladder.—This condition is now recognized as occurring with greater frequency than used to be considered the case. McAdam Eccles[23] states that protrusion of the urinary bladder into the hernial sac is not of very rare occurrence, for it is probably to be found associated with nearly one per cent. of inguinal herniæ.

The entire bladder and prostate may be found outside the abdominal wall, either enveloped in a true peritoneal sac or only partially covered by peritoneum. The commonest form of vesical hernia, however, is that in which the inner wall of the sac of a direct or indirect inguinal hernia is partly represented by the peritoneum covering the posterolateral aspect of the bladder.[24]

A third variety is that in which the bladder descends without any peritoneal covering at all.

The symptoms of such a condition are with two exceptions of not much value, the fact that the condition is not usually recognized except during the course of an operation emphasizing this fact.

The two points of value in the diagnosis are first that the inguinal tumor can be made to disappear by the patient micturating, and that the swelling on being reduced by the hand causes the patient the most intense desire to pass urine. In certain very exceptional cases a catheter may be passed into the portion of bladder lying in the sac, and this would at once render the diagnosis certain.

The only two lesions for which the condition could be mistaken when it is fully developed are hydrocele of a hernial sac and an ordinary vaginal hydrocele.

Treatment of this condition is upon very definite lines. The bladder must be separated from the hernial sac if possible without being

opened. If it is opened, accidentally or purposely, the wound must be carefully closed, the sutures not penetrating the mucous membrane, and replaced in the abdomen. If the peritoneum over it is wounded it should be closed by a series of sutures in the ordinary way.

The danger of the condition lies in the fact that it may be accidentally wounded. It may be tapped on the supposition that the operator is dealing with a hydrocele, or the real character of the swelling may not be appreciated when an operation is performed, the contained urine being mistaken for the fluid found sometimes in the sac of a hernia.

Stone in the Bladder.—In an article which appeared in the *Lancet*[25] I endeavored to illustrate the progress which has been made in recent years in the treatment of stone in the bladder by a series of over one hundred cases operated upon by litholapaxy alone. An analysis of these cases showed that while the mortality was under six per cent., the recurrences reached the high figure of nearly twenty-three per cent. This aspect of the question has already been treated by me in more than one contribution to surgical literature,[26],[27] but in the past seven years I am inclined to think that the causes underlying recurrences of this nature have come to be better understood.

The age in the twenty-three cases I referred to averaged sixty-three years. In seventeen instances considerable enlargement of the prostate was present, as one would expect at such an age, twelve had pouched bladders, and the same number were dependent upon their catheters to a very large extent at the time of operation. In two cases it seemed probable that recurrence was due to fresh descents of stone from the kidneys and their retention within the bladder by the large prostate. In one of the fatal cases recurrence was traceable to a pouched bladder complicated with chronic urethral stricture and suppurative nephritis. Hence it may be inferred that though a stone is successfully removed by operation, this does not necessarily imply that the original cause for its production has ceased to exist. In this class of cases the liability to recurrence after a crushing operation seems in some degree to discredit Bigelow's method in the eyes of the profession and public. Mr. Cadge, of Norwich, referred to the matter in 1886 in the following terms: "This seems a heavy indictment to bring against lithotrity, but I am afraid that there is no gainsaying it, and if so it would be wrong to pass it over or make light of it. Many of these relapses might be prevented if the patients would observe directions and persevere with treatment."[28] These remarks are as true to-day as they were sixteen years ago, but experience confirms me in my belief that recurrence *need not* be any more common after litholapaxy than after any other operation, having for its object the simple removal of the stone. The prevention of calculus recurrence depends on (1) the

local treatment of the bladder after the operation; (2) preventive treatment based upon the mode in which it is assumed that urinary calculi are formed.

The Local Treatment of the Bladder following Litholapaxy.—In cases in which the normal functions of the bladder are impaired by prostatic obstruction personal supervision should be exercised after the patients have passed from the hands of the operating surgeon into those of the usual medical adviser. In many such cases small calculi descend from the kidneys into the bladder, and are quite capable of removal by washing out, although the bladder with its powers weakened or its outlet obstructed is not able to void them unassisted. In other cases, owing to long-standing cystitis, the urine does not regain an acid reaction, and there is a great tendency to the formation of phosphatic "grit" and débris, largely composed of the triple phosphates so freely deposited in alkaline urines. In either case the indications are for careful and systematic washing of the bladder.

For this purpose a large metal syringe, holding from four to six ounces of solution, is most useful. The plunger should move easily, and the nozzle should have a large bore and be conical in shape to fit various sizes of catheters. The best catheters for the purpose are large bore (about twelve to fourteen English scale) silk web instruments with a large, smoothly bevelled eye, the end of the instrument beyond the eye being solid. Considerable flushing and sluicing of the bladder can be attained with such instruments. The practitioner should wash out the patient's bladder three or four times a week. A useful manœuvre consists in injecting from five to ten ounces of solution and then directing the patient to roll over on to his abdomen and in other directions. By this means débris lodged in small sacculi and post-prostatic pouches will be dislodged, and upon inserting the catheter again will be ejected with the stream of lotion. In addition to this washing it is well in such doubtful cases for the patient to pay a visit at intervals of about a month to six weeks to the operating surgeon for the purpose of having the bladder thoroughly evacuated by the lithotrity evacuator and evacuating catheter, instruments which the practitioner does not usually possess. It is not possible to indicate precisely how long the local measures described must be continued or how often repeated. The absence or the presence of the symptoms referred to in individual cases should determine these points.

Preventive Treatment having Regard to the Probable Mode in which Urinary Calculi are Formed.—An uncleanly condition of the urine, particularly of residual urine, when the individual is more or less dependent on the use of the catheter, is often a contributory cause of ammoniacal decomposition and the recurrence of stone after operation. I say a contributory cause, as some seem to doubt that a phosphatic

stone can be formed without the presence of a nucleus upon which concretion can take place. But phosphatic stones frequently form in the bladder, having no discoverable nuclei other than the mixture of triple phosphates and sticky mucus which is the usual starting-point of one of these "dirt stones." The process of molecular coalescence [29] is sufficient to explain this fact. Much may be done under these circumstances to prevent urinary decomposition by the use of the catheter and syringe as already referred to. Within the last few years many valuable drugs have been introduced for the purpose of sterilizing the urine.

Some years ago I drew attention to an easily soluble and digestible salt of boric acid which often answers admirably, and is much used by itself and in combination with other drugs. It is known by the name of borocitrate of magnesia and may be taken frequently with some powdered sugar in teaspoonful doses in a tumblerful of water.

An invaluable drug in the treatment of these decomposing urines is that known as urotropin. It may be taken in ten-grain doses freely diluted with water, either singly or in combination. A formula which has proved most serviceable in my hands is the following:

℞ Ammon. benzoat., ... gr. xv.
Acid. boric., ... gr. x.
Urotropin., ... gr. x.
Aq. chlorof., ... ʒi.
M. S. To be taken in half a tumbler of water thrice daily.

It must not be lost sight of, however, that urotropin if given in large doses for long-continued periods may cause some irritation of the kidneys and bladder,[30] in the former instance actually going so far as to induce slight hæmaturia, consequent no doubt upon a semi-acute nephritis.

Another valuable drug in the same connection is cystamin, which given in the same doses does not appear to cause the same amount of irritation as urotropin; at all events I have not remarked any ill effects from it in my own practice, nor am I acquainted with any recorded observations of such a nature.

Vesical Stone in Children.—The application of the principles of litholapaxy to the treatment of stone in the bladder in male children is due to the enthusiastic advocacy of the method by surgeons of the Indian medical service, particularly Surgeon-Colonel Keegan and Surgeon-Colonel Freyer.

The results of lithotomy in children had been so excellent that there was a strongly rooted prejudice against the substitution of the crushing operation for a measure which had proved so satisfactory, but the publication of two papers by Keegan [31] in 1885 gave a great stimulus to litholapaxy, and when the results subsequently obtained by Freyer [32, 33]

also became known the operation began to take its proper place in the surgery of stone in young children.

At the present date the practice of all surgeons of experience in this class of cases is to perform litholapaxy except when contraindicated by circumstances which I shall mention. The first essential in the performance of litholapaxy in children is the possession of proper instruments. Keegan writes: "Unquestionably the best, and indeed the only perfectly safe form of lithotrite to use in performing litholapaxy in young boys is the completely fenestrated pattern of lithotrite."[1]

Freyer says that "The surgeon should be provided with a series of small, fully fenestrated lithotrites of the same patterns as those used for adults, but varying in size from No. 5 to No. 10. It will be found that in boys aged from thirteen to sixteen years a lithotrite of size No. 11 or 12 will pass readily as a rule. The cannulæ employed are also similar in shape to those used for the adult, but vary in size from No. 6 to No. 12 English scale. The smaller sizes should not be more than seven inches in length, as the return stream through these small cannulæ is very weak and diminishes in strength with the length of the tube. The aspirator is the same as for adults, but it must of course be worked very gently, only a small quantity of water, proportional to the size of the bladder, being thrown in."

Owing to the small size of the evacuating catheters used it is essential to break the calculus into extremely fine débris. Hence considerable patience is necessary, and a good deal of tactile and manipulative skill, for the small size of the lithotrite makes the crushing difficult in proportion to the size of the stone.

No force should be used in introducing the instruments. If force is necessary to pass the smallest instrument at hand, then the operation should be abandoned in favor of lithotomy or postponed until instruments of a proper size can be obtained.

Turning to a consideration of the results of litholapaxy in young children we find that the operation has been practised with complete success at the early age of eighteen months. From then onward the difficulties of operating decrease with the increase in age. Between the years 1885 and 1896 Freyer, practising in India, performed the operation one hundred and sixty-five times with only two deaths. The opportunities in Great Britain are not numerous, for stone in the bladders of young children is not a common complaint. I have operated on several cases in the past few years, without difficulty and without any fatal result. Cure has in each case been rapid and no untoward symptoms have developed.

When we consider that the period of convalescence after litholapaxy is, in an uncomplicated case, at the most four to seven days, and compare this period with the fourteen to twenty-one days necessary

after lateral or suprapubic lithotomy, the advantage of the operation is evident. That there is still a large number of surgeons who cling to lithotomy is quite true, but they are found only in the ranks of those who, however large their practice may be in general surgery, have had but little experience in genito-urinary work, and who therefore have not had the opportunity of testing a method which is so thoroughly accepted by those most competent to judge of its adequacy and safety.

The factors which contraindicate the operation of litholapaxy in young children should be well appreciated, for disaster will follow the operation if it is performed in an unsuitable case.

In the first place the operator must be experienced in the use of litholapaxy instruments, for although the operation in the hands of a surgeon skilled in this particular class of work appears extremely easy, the beginner will find that this simplicity is only apparent even in the case of adults, and in children the greatest delicacy of manipulation is necessary.

Great size of the calculus in relation to the size of the bladder is another contraindication to the operation. In adults a stone of practically any size can be crushed, for although the lithotrite may not be able completely to *grasp* the stone at first, it can break pieces from it until the circumference is such that the stone can be seized in its smallest diameter and broken across.

Such a manœuvre as this is not permissible in the case of large stones in young children, for the bladder walls are so delicate that the bruising to which they would necessarily be subjected by the movements of the lithotrite in so confined a space would prove a source of very serious danger.

An ample supply of suitable instruments is absolutely essential, and when there is any doubt upon this point another operation should be chosen. It cannot be too strongly emphasized that no force is admissible in the passage of litholapaxy instruments, in the case of children especially, and if any difficulty is experienced with the instruments at hand the operator should not hesitate to convert a litholapaxy into a lithotomy.

In concluding these supplementary remarks I desire to express my indebtedness to Mr. J. G. Pardoe, now on the staff of St. Peter's Hospital, for much valuable assistance.

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DISEASES OF
THE URETHRA AND PROSTATE GLAND.

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THE URETHRA.

THE principal advance in urethral pathology since the appearance of the first volume of the TWENTIETH CENTURY PRACTICE, in 1895, has been the establishment of the relation of deep-seated and excessively chronic infection of the glandular tissue and adnexa of the prostate to chronic urethral disease. While a more thorough knowledge of prostatic infection and its results has led to a somewhat pessimistic view, in general, of the curability of chronic deep-seated gonorrhœal infection, it has nevertheless greatly increased the usefulness of the surgeon in this field. We are now fairly conversant with the unfortunate pathological fact that chronic urethral discharge and recurrent infection in the male, to say nothing of the various forms of infection conveyed to innocent women, are often due to deep-seated prostatic disease of long standing, with or without associated infection of the vesiculæ seminales. With increasing knowledge of the pathology of deep-seated gonorrhœal infection, we have come to understand, first, the incurability of the majority of such cases, from a pathological standpoint, however good the clinical result may seem to be; second, the necessity of persistent antiseptic, *i.e.*, microbicidal, treatment of such conditions, associated with the mechanical expression of the diseased secretions and a modification of the perverted circulation of the part by prostatic massage.

Prostatic Massage.—In a general way the treatment of chronic posterior urethritis of gonorrhœal origin involves also the treatment of chronic gonorrhœal prostatitis, as they are almost invariably associated. It is here that the comparatively new treatment by massage of the prostate comes into play. In comparatively few cases of deep-seated infection is it possible for the surgeon to do the case full justice without thorough and systematic massage, continued for a prolonged

period. By massage we accomplish, as already suggested, the expression of the germ-laden pathological secretions of the affected glandular tissue, and an improvement in its circulation. Not only is the circulation temporarily stimulated and permanently improved, but the massage has a distinctly deobstruent effect upon the diseased tissues, inducing absorption of the inflammatory exudate, which is always present and enters into the *ensemble* of pathological conditions found in prostatic and periprostatic hyperplasia. Irritability of the prostate and vesical neck is distinctly relieved by massage. This is brought about in two days: (1) Through the improvement in the circulation and the removal of the exudate which produces irritation of the delicate nerves of the part; (2) by directly blunting the sensitiveness of the nerve supply, thus relieving hyperæsthesia and assisting in restoring the sensibility to its normal status.

The general effects of prostatic irritation, especially in those cases in which hyperplastic or inflammatory tissue is exerting constant pressure upon the sympathetic and sensory nerve supply, are much more marked than is ordinarily supposed. Neurasthenia of the ordinary type, and sexual neurasthenia, with its manifold symptomatology, embracing digestive disturbances, bowel inactivity, melancholia, hypochondriasis, and that seldom recognized but frequent condition, male hysteria, are among the results of chronic prostatic disease which are frequently relievable by proper and systematic massage.

In a general way, the author does not hesitate to assert his belief that massage of the prostate, properly performed, is one of the most valuable advances in genitourinary therapeutics that have been developed for many years. Prostatic massage is not to be considered a cure-all, but it should always be given a fair chance. Many individuals labor under the idea that they are administering massage of the prostate when, as a matter of fact, the treatment which they are giving is as far removed from scientific prostatic massage as could well be imagined. The surgeon with the short, stubby finger would better dispense with the treatment altogether, rather than to bring it into discredit through failures in cases in which, were massage properly performed, excellent results would be obtained. In many instances the physician undertakes massage of the prostate without in the least crystallizing in his mind the anatomical points necessary to the intelligent employment of the treatment. The author has met with numerous cases in which so-called prostatic massage consisted in rubbing the perineum. Comment upon this is unnecessary.

In the performance of massage of the prostate various authorities recommend different methods and positions. In my experience the lateroprone position, with the buttocks upon the edge of the table so as to be easily accessible to the operator, and the knees well drawn up

toward the chest, is most satisfactory. It is as difficult to instruct the inexperienced in the technique of prostatic massage as it is to describe the sound of a violin. Much depends upon the tactile sensibility and education of the finger. In a general way, prostatic massage requires that not only the prostate proper, but the periprostatic tissue should be stroked and rubbed with the pulp of the finger toward the median line, and forward toward the operator. The seminal vesicles, the prostate, and the periprostatic tissue at the neck of the bladder represent an equilateral triangle, the apex of which corresponds to the apex of the prostate and the base to a line drawn between the upper extremities of the seminal vesicles. The massage should be applied obliquely toward the median line and apex of the prostate. As a rule, all of the tissues within this triangular area should be thoroughly massaged. The amount of pressure depends upon the tolerance of the patient, the sensibility of the prostate, and the chronicity of the inflammation. It should be gentle at first, and gradually increased *pari passu* with the increase in the tolerance of the patient.

The frequency with which massage should be administered necessarily depends upon circumstances. Some patients tolerate the operation daily with manifest advantage. Comparatively few, however, tolerate it oftener than every other day, and in by far the majority of cases twice weekly is best. The massage may be combined with through-and-through irrigations of various solutions, of which the permanganate of potassium, nitrate of silver, albargin, and sulphate of copper are the most useful.

Silver Injections.—The last few years have been signalized by the introduction of a class of remedies for gonorrhœal infection which constitute a distinct advance over all those hitherto employed. The colloidal salts of silver have admirably stood the test of time and experience in the treatment of gonorrhœa. The most useful of these salts are argonin, protargol, albargin, and nargol. The majority of genitourinary authorities claim preëminence for protargol, and many use it to the exclusion of all the other silver salts. Without discussing in detail the merits and demerits of the various preparations of silver, the author will briefly present the conclusions which he has drawn from his rather extensive use of them. The new salts of silver, like the nitrate of silver, are distinctly gonococcidal in their action. So marked is their destructive influence upon the gonococcus that, were it anatomically possible to reach by any known method of application every portion of the area infected, it would be possible to cure by a single application of a solution of any of these salts, in moderate strength, any given case of gonorrhœa.

The order of the usefulness of the silver salts, so far as the author's own experience goes, corresponds to the order in which they have been

enumerated above. Argonin is the most serviceable, the difference, however, between argonin and protargol being not very marked. Albargin has proved a very valuable addition to the therapy of gonorrhœa. It is more irritating, however, than the other salts, but, if used in mild solutions, is especially advantageous in the declining stages of urethritis, and for irrigation in chronic infections, particularly of the prostate and bladder. In simple urethritis, *i.e.*, urethritis of non-specific origin of a subacute or chronic character, it is very valuable. It may be used in the strength of from one-fourth of one per cent. to two per cent. When used by irrigation, it must be remembered that, like the nitrate of silver, it is proportionately much more irritating when copious quantities of a very mild solution are used than when small quantities of much stronger solutions are used. Mild irrigation is often productive of much more irritation than the injection of quite strong solutions by the ordinary deep urethral syringe. Argonin and protargol should be used in a strength of one-half of one per cent. at the beginning of treatment, being gradually increased in strength thereafter. It is rarely necessary to increase the strength beyond two and a half or three per cent.; indeed, comparatively few patients tolerate a strength of more than four per cent. As the gonococci begin to disappear from the discharge, an astringent, such as the muriate of hydrastin, may be added to the solution of the silver salt. Nargol is rather less irritating than the other silver salts, but, so far as the author's experience goes, not so universally useful. Increasing experience, however, may modify this opinion.

Urethral Irrigation.—A distinct advance in the management of urethral disease and the prostatic and vesical complications or conditions secondary to urethral disease, has been the introduction of the irrigation method, or, rather, its general recognition. This qualification is only just, for the reason that the author was using through-and-through irrigations of permanganate of potassium in deep-seated gonorrhœal infection more than twenty years ago. So far as he is aware, the first contribution which appeared in this country on the treatment of deep-seated urethral and bladder disease by means of copious irrigations, without the use of tube or catheter, relying entirely upon hydrostatic pressure, was written by the author, and published some years ago in the *Journal of Cutaneous and Venereal Diseases.* Credit for the method has, within the last few years, been given to Janet, where it has not been deliberately appropriated without credit. Reverdin, however, in Europe, antedated Janet in the use of this method. The credit for its general use in America belongs to Valentine.

As has been said of the silver salts, copious irrigation with permanganate of potassium solution is so nearly a specific for gonorrhœa that a single treatment would suffice for the cure of the disease in un-

complicated cases were it not anatomically impossible to treat all the affected tissues, and bring the antiseptic solution in contact with each individual germ. Permanganate of potassium is the most generally useful of all the drugs that have been used for irrigation of the urethra, prostate, and bladder in gonorrhœal infection. The colloidal silver salts, however, are of great value, and were it not for the important consideration of their costliness, as compared with the permanganate, they would be more extensively employed than they are. Permanganate of potassium should be used at the beginning of treatment in moderate strength, much being dependent upon the stage of infection and the tolerance of the urethra. A strength of 1–10,000 to 1–7,000 is usually sufficient at the outset, the strength being gradually increased until as high as 1–1,000 is reached in some cases. If the method be used at all, it should be used systematically and frequently. It is applicable only in chronic and subacute cases. It is especially valuable in incipient gonorrhœa, in which the disease can hardly be said to have fairly begun. It is often advisable to begin by a thorough irrigation, twice daily, this being employed for a week, at the end of which time a single daily irrigation is given. The treatment should be kept up for at least three weeks in recent cases. In many cases treatment must be continued much longer.

In chronic cases either the permanganate or some other gonococcidal drug must be employed until the germs have entirely disappeared.

The recurrent catheter or tube is now seldom used for irrigation. A short nozzle of some kind is indicated. The author has found a simple hard-rubber nozzle, of his own designing, to be the most generally useful for the purpose. The Valentine apparatus is excellent, however. Care should be taken not to have the hydrostatic pressure too great. Two things should be avoided: (1) The entrance of fluid into the deep urethra in cases in which these parts are not already infected; (2) trauma of the urethra produced by the pressure of the entering fluid.

In very acute and virulent cases, the irrigation method should not be employed until such time as the inflammation has in great measure subsided. Very serious results sometimes accrue from neglect of this precaution. In chronic cases involving the deep urethra, prostate, and bladder, through-and-through irrigation is required. The antiseptic solution is forced into the bladder by simple hydrostatic pressure, to be expelled thereafter by voluntary micturition. Care should be taken to irrigate the anterior urethra thoroughly before allowing the fluid to enter the deeper portion of the canal, lest more severe deep-seated infection occur than that which already exists. A liberal quantity of fluid should be used—from a quart to two quarts. This

should be given moderately warm. It should be remembered that very hot solutions may destroy the epithelium of the mucous membrane of the genitourinary tract without producing the least discomfort to the patient. The patient's sensations, therefore, are no criterion for the guidance of the operator.

After the anterior urethra has been thoroughly irrigated by the ingress and egress of the major part of the antiseptic solution, the bladder should be filled from two to four times, and the patient instructed to expel the fluid, as in micturition. Care should be taken not to overdistend the bladder, for it is quite easy to traumatize it by hydrostatic pressure.

A method of treatment for chronic urethral disease which has recently become quite popular in certain quarters is that of Oberlaender. This consists in systematic dilatations of the urethra by means of dilators or "expanders," constructed especially for the purpose. These are of two varieties, adapted to the anterior and posterior urethra respectively. These systematic dilatations are combined with through-and-through irrigations with antiseptic solutions, permanganate of potassium having the preference. The method is of distinct value, when the patient is able and willing to submit to its systematic employment. Like most therapeutic innovations, too much has been claimed for it by its overzealous advocates. Discounting this, however, many cases which have proved resistant to other measures of treatment are unquestionably amenable to it.

Urethroscopy.—Increasing experience in urethroscopy has only served to demonstrate the value of accurate localization in the diagnosis and treatment of urethral disease. The time has passed when it is either scientific or practical to go on indefinitely treating chronic urethral disease without careful investigation to determine the fundamental pathological conditions present. Not infrequently the ordinary means of treatment have been persisted in for months, or perhaps years, without avail, in cases in which urethroscopy has readily determined the existence of an extremely limited area of disease, the treatment of which has resulted in the cure of a chronic discharge of long standing.

The author's personal experience has confirmed him in the view, expressed many years ago, that, in order to do successful urethroscopic work, it is necessary to use tubes of rather large calibre. The use of small tubes for the exploration and treatment of wide-calibred urethras seems the height of absurdity. The profession of Europe—the fountainhead of urethroscopy—seems woefully behind that of America in this essential. As time goes on, the importance of the teachings of Fessenden Otis, in regard to the relation of the calibre of the urethra to disease of its mucous membrane, seems more and more

evident. In cases in which the urethra does not admit urethroscopic tubes of some size, pathological obstructive conditions necessarily exist, which demand removal independently of any possible revelation that may be made by urethroscopy. Once the coarctations of the urethra have been removed, the necessity of urethroscopic diagnosis and treatment ofttimes no longer exists.

Urethrotomy.—There has been something of a reaction on the part of the profession against the operation of internal urethotomy in recent years. This reaction has been, to a certain degree, ill-timed and based upon false premises. It has been supposed—nay, claimed—in certain quarters that the introduction of the Oberlaender method, combined with through-and-through antiseptic irrigation has done away with the necessity of internal urethrotomy. To this view the author respectfully demurs. It is undoubtedly true that a more systematic use of dilatations, combined with suitable irrigation, than has hitherto prevailed will somewhat lessen the number of strictures developing from gonorrhœa. That the method is much, if any, more efficacious in the management of stricture, once that condition has developed, than the ordinary methods of dilatation, combined with antiseptic irrigation, seems to the author's mind very doubtful. So far as resilient and irritable strictures are concerned, the Oberlaender method of treatment is often deleterious rather than otherwise, and the patient is eventually compelled to submit to operation.

THE PROSTATE.

While the surgery of the prostate has not yet assumed its proper position as a field for classical surgical technique, the past ten years have witnessed marked advances in this direction. Should the same rate of progress continue for another decade, hypertrophy of the prostate and kindred conditions will no longer be the *bête noir* of the surgeon and the despair of the afflicted patient. A distinct advance in our knowledge of prostatic pathology and therapeutics has been the steadily growing belief that in a large proportion of instances the so-called senile disease of the prostate is due to chronic congestive and inflammatory conditions, developing at a period remotely antecedent to the appearance of the first definite symptoms of mechanical urinary obstruction. Many years ago the author expressed his faith in this view of prostatic pathology, and he believes that he is justified in saying that he was a pioneer in this field. Chronic hyperplasia following congestion from various causes was advanced by him as the cause of many cases of prostatic hypertrophy. With increasing experience this view has been confirmed, and modified only to the extent of believing that distinct chronic inflammatory changes are sometimes the

basis of so-called senile prostatic disease. Careful macroscopic and microscopic examination of a large number of both healthy and diseased prostates has served to crystallize the author's original impressions upon this point.

The importance of a knowledge of the congestive and inflammatory factors in the etiology of prostatic disease is at once obvious. While prostatic hypertrophy and its congeners are insusceptible of relief save by radical surgical procedures, the same cannot be said of the fundamental conditions from which, according to the author's view, chronic prostatic disease develops later in life. In many instances the cause of the primary hyperplasia and inflammation of the prostate is some irritative affection of the prostatic urethra, or even of the pendulous urethra acting reflexly. By attention to these conditions, prostatic hypertrophy may be prevented in a certain proportion of cases. The indications in this direction are:

1. To educate the profession and the public to an understanding of the fact that so-called senile hypertrophy of the prostate is not a disease necessarily incidental to senility—not a part, so to speak, of perverted senile physiology, but is due to causes and conditions operative at but middle life, or even long before that period—causes which may often be either removed or so far inhibited that serious chronic disease, which will otherwise inevitably occur later on, is prevented. A point of great importance is the necessity of an early diagnosis and careful methodic treatment as curative of present conditions, and prophylactic of much future misery.

2. The second indication is to relieve by suitable systematic treatment by sounds, irrigations, and antiseptic, astringent, or alterative applications irritative affections of the vesical neck in the male. It is obviously necessary to remove all sources of irritation and infection, no matter what portion of the urethra may be involved.

3. The third indication is to remove congestion of the prostate and its environs, and stimulate absorption of the hyperplasic or inflammatory exudate. This may best be done by massage.

The author, some years ago, took the position that residual urine *per se*, which has been the bugbear of the profession from time immemorial, was not so pernicious as ordinarily believed, so long as it was aseptic. The passing years have only confirmed his views upon this point. In a general way, it is safe to assert that the prostatique's period of greatest danger begins when he first consults the surgeon and is advised to catheterize himself systematically, or have the operation performed by the physician, for the purpose of withdrawing residual urine. More harm has resulted from the exaggerated estimate of the importance of urinary residuum in prostatic disease, on the part of both the profession and laity, than from almost any other fac-

tor that could be mentioned. An endeavor to relieve prostatic congestion and irritation of the vesical neck is rational. The mere frequent withdrawal of the residuum, with its attendant dangers of infection and the establishment of the catheter habit, is decidedly irrational, so long as the residual urine is in moderate amount and aseptic. Just as soon, however, as sepsis occurs and the residual urine is converted into a highly septic fluid, as is inevitably the case when it becomes infected, systematic vesical evacuation and irrigation are necessary in all cases in which the patient will not submit to a radical operation. The benefit derived from catheterization, when the residual urine is perfectly healthy, is not due to the withdrawal of the fluid *per se*, but to the blunting of the hyperæsthetic sensibility of the delicate nerves supplied to the prostatic urethra by the passage of the catheter. The same result will occur from the passage of a solid bougie or sound, a much safer instrument than the catheter, or from the application of nitrate of silver solutions of varying strength to the *pars prostatica*.

It is well, in considering the advisability of the adoption of palliative catheter treatment in prostatic hypertrophy, to consider the average duration of life in patients who have once adopted the systematic use of that instrument. Mr. Reginald Harrison states that the average duration of catheter life is four years. I believe that this estimate is rather under the mark. I should say, from my own experience, that the period is about five years. The profession is wont to allow its judgment to be perverted by the occasional case of the old man who has passed the catheter, with impunity and comfort, for many years, apparently without any resulting pathological conditions. These are the exceptions, which merely serve to prove the rule, and should be placed in the same category as the man who carries his catheter in his trousers pocket, and who, without ever boiling or otherwise aseptizing the instrument, passes it into his bladder at frequent intervals after lubricating it carefully with his own saliva. It is a singular fact that physicians and surgeons who would never think of scorning asepsis and antisepsis because of the occasional case of the fool who rushes in where angels would fear to tread, nevertheless base their advocacy of the routine use of the catheter upon occasional cases of prolonged catheter immunity such as those above mentioned. It must be remembered that once the prostatique becomes addicted to the use of the catheter, he must continue it the rest of his life. That his days are likely to be short is shown by what has been said on the subject of the average longevity of men with the catheter habit.

Three very important points that should be impressed upon the prostatique are: (1) That if palliative measures, instituted at a relatively early period, do not inhibit the development of prostatic over-

growth, a slow but sure increase of the enlargement is inevitable, and a change in the conformation of the prostatic urethra, with obstruction of the urinary way, is almost certain. (2) That the time will inevitably arrive when he will be compelled to take his choice between the habitual use of the catheter, which will almost of necessity shorten his days, and a radical operation for the relief of the prostatic obstruction. (3) That early operation, before the occurrence of septic and obstructive changes in the urinary way, which always develop sooner or later, is comparatively safe, the reverse being true when he is faced with an operation of necessity.

The time is not far distant when the surgery of the prostate will occupy as exalted a plane as ovariotomy. In the days when ovariotomy was performed only as a *dernier ressort*, and in cases which must inevitably have proved fatal without it, the statistics of the operation were by no means flattering. Time has changed the position of the profession regarding ovarian tumors. An attempt is made nowadays to diagnose them early, and the period of election for operation is synchronous with the establishment of the diagnosis, or the discovery of such conditions as warrant an exploratory operation. The favorable statistics of ovariotomy are now familiar to every one in the profession, and are very flattering to the enterprise and skill of modern surgery, and of American surgery in particular.

How different the picture presented by the surgery of the prostate! The genitourinary surgeon is confronted, on the one hand, by the ignorance of the laity, an ignorance for which the profession is itself responsible, and which leads the layman to believe, when he develops in advanced life the symptoms of urinary irritation and obstruction, that he is suffering from something which, as he expresses it, "every old man has," and, upon the other, with the fatuous notion of the profession at large that the disease is not only an inevitable consequence of senility, but is remediable only by means of the systematic use of the catheter. The consequence of this ignorance is that cases are submitted to operation only when they have become so desperate, and the suffering is so great, that for humanity's sake something must be done. The period of election for operation in prostatic disease should be the earliest moment after the condition has been diagnosed, and measures prophylactic of serious increase in the size of the growth have been shown to be inefficacious. A radical operation should be performed before serious secondary infection and pressure changes occur in bladder, ureter, and kidney. These changes will inevitably occur if the condition be allowed to go on, and, irrespective of what uranalysis shows, the probability of their existence in greater or less degree should be taken into consideration in every case of chronic obstruction of the urinary way. The period of election once estab-

lished, and radical operation upon the prostate being done at a time when the bladder and kidneys are comparatively healthy and free from infection, we shall have some statistics on prostatic surgery worthy of attention. The statistics thus far presented do not show what can be accomplished by rational surgery of the prostate. They simply demonstrate that a certain number of patients do recover from operations performed upon the prostate under the most unfavorable circumstances. The author is of opinion that the statistics of radical operations upon the prostate thus far presented are of no particular value, and are absolutely no criterion of the relative mortality or success of the operation *per se*. Early diagnosis, followed in some cases by judicious means of palliation, or of prophylaxis of permanent change of the prostate, and failing of success with these measures, a radical operation—prostatectomy—should be the guiding principles in prostate surgery.

The technique of operations for prostatic disease has changed somewhat within the past few years. The popularity of some procedures has increased, while that of others has waned. When the first volume of the TWENTIETH CENTURY PRACTICE appeared, the author's views upon the Ramm-White operation of castration for prostatic disease were very conservative, despite the multitudinous reported cures by the operation. The author to-day congratulates himself upon the conservatism which he exhibited at that time—a conservatism which was rather harshly criticised in certain quarters. The various mutilating operations upon the testes and cord have fallen into comparative desuetude. They have a limited range of application, it is true, but it is chiefly as tentative procedures, in cases in which a rational radical operation is contraindicated or refused, that such operations are warrantable. There can be, however, under proper circumstances, no serious objection to their tentative employment—always providing the sexual powers have already been lost.

The most rational method of dealing with prostatic hypertrophy and its congeners is the radical operation of prostatectomy. The suprapubic method was, until recently, the most popular form of operation, and is the one which the author has most often performed. He has, however, performed at various times, for some years, in suitable cases, the perineal method of prostatectomy, the principles of which are the same as those of the old perineal prostatectomy of Dittel. There has recently been an attempt in certain quarters to establish this as a new operation. It is not only not new, but, despite certain modifications of its technique, it is a lineal descendant of Dittel's old-time method. It is claimed by some of the more enthusiastic advocates of the method of perineal prostatectomy that it is applicable in all cases. This the author does not believe to be true. Many cases

occur in which it is an utter impossibility to perform a thorough and complete operation by the perineum. It should be the operation of election when the tumors are accessible. When the patient has a short, deep, fat perineum, and the prostatic overgrowths are, in the main, intravesical, it is sometimes an utter impossibility to operate by the perineal route. The suprapubic method, or the combined perineal and suprapubic method, therefore, must be selected in such cases.

The electrocautery operation of Bottini, recently revived, has been very enthusiastically boomed in certain quarters as the routine operation in chronic prostatic disease. If one were to judge from many of the published reports of results of the Bottini operation, he must needs conclude that a method of treatment has been discovered which has revolutionized not only the surgery of the prostate, but the pathology and morbid anatomy of prostatic disease. It must be remembered that, no matter what operation is performed in advanced prostatic disease, certain secondary pathological conditions necessarily exist which have developed as a consequence of (1) urinary pressure and (2) infection.

The most striking feature of much of the reported clinical experience with the Bottini operation, especially as bearing upon its remote results, is that the incurable secondary conditions in prostatic disease, which very often defeat the object of the surgeon who employs other radical methods of dealing with the obstruction, do not seem to exist in the patients operated on by the electrocautery method. The author believes he is safe in saying that no operation performed in advanced prostatic disease will subvert the old familiar pathology of the disease and its secondary conditions to the very laudable desire of the surgeon permanently to relieve his patients. It must be remembered that, no matter what operation may be instituted for the radical cure of chronic prostatic disease, the surgeon who operates upon advanced cases is inevitably confronted with secondary conditions and complications that must necessarily modify the benefits which would otherwise be derived from a radical operation, if indeed they do not defeat the object of the surgeon altogether.

We have just cause for suspicion of the reports of radical operations on the prostate, of any kind whatsoever, which have resulted in so many recoveries that, in order to achieve such results, the every-day pathology and morbid anatomy of enlargement of the prostate and its secondary results and complications must necessarily be done away with for the special benefit of certain operators. Some very brilliant results from the Bottini operation have been reported, but it is noteworthy that the earliest, most multitudinous, and most brilliant reports emanated from the men of least experience.

The safety of the operation has been exaggerated. Often only the immediately favorable results have been reported. It is only recently

that the more conservative and philosophic men of the surgical profession have begun to appear in print with cases which seem to establish the value of the Bottini method in suitable cases beyond peradventure of doubt.

The author will attempt to forestall, in a certain degree, the adverse criticism which the foregoing remarks are likely to bring forth, by calling attention to the somewhat sinister fact that the brilliancy of the results thus far reported from all quarters in which the Bottini operation has been advocated, can be compared only to that of the multitudinous reported operations of the Ramm-White method, with which the journals teemed a few years since.

The modification of the Bottini, suggested by the author when the operation was first revived, by operating through a perineal incision so as to give an opportunity for drainage and tamponnage in case the latter are necessary, is attaining some popularity in certain quarters, and is a much more rational procedure than the Bottini operation proper. The truth of this statement can be made apparent only when the various fatalities incidental to the orthodox Bottini operation have been frankly and conscientiously reported. Whatever may be claimed for the Bottini operation, this much, at least, may be said: It is a surgical operation performed in the dark, and one which does not conform to the requirements of modern aseptic and antiseptic surgery, in that it does not provide for drainage or for the proper control of possible hemorrhage. That these objections are not theoretical is shown by incidental and accidental developments in the results of certain operators who perform the Bottini operation as a matter of routine.

A serious objection to the Bottini operation is that it is likely to be reserved for late cases, thus retarding the development of prostatic surgery in general. The rational surgery of the prostate demands an early radical removal of the tissue overgrowth which is the essence of the disease. Prostatic surgery must advance along these lines. It is admitted that there are certain cases in which the Bottini operation is especially applicable—cases in which there is a distinct median bladder obstruction of limited extent, and in which one or multiple incisions with the galvanocautery will suffice to free the vesical outlet and afford efficient bladder drainage; but in by far the majority of cases in which distinct prostatic tumors exist the only operation which is rational is the radical removal of the morbid tissue. If this procedure be rational, it only remains to make it as safe as other operations of like importance. This, the author believes, can be done, but only by early diagnosis and early operation. What is most needed is a general recognition of the necessity and wisdom of early prostatectomy—prostatectomy at a period when we have no secondary conditions to deal with.

CHEMICAL AND MICROSCOPICAL

EXAMINATION OF THE URINE.

BY

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Alcaptonuria.

ALCAPTON, $C_6H_4(OH)_2$, is a crystalline body found in the urine, probably as a result of a decomposition of proteids. Its importance in uranalysis is due chiefly to the fact that it may cause deception in the use of the sugar tests. Its presence becomes known from a spontaneous change of color after exposure to the air. The appearance of the urine when voided is normal, and it remains so if protected from the atmosphere. If exposed, the surface becomes a dark brown and the color gradually extends to the entire specimen. It may be readily differentiated from glucose by the absence of reaction to the fermentation test and by the fact that it possesses neither dextrorotatory nor lævorotatory power. Fehling's solution is reduced only with the aid of heat. The brown color is intensified by the addition of an alkali and the ammoniacal silver solution is rapidly reduced without heat.

Test.—Add to the urine to be tested one drop of a very dilute ferric chloride solution (the liquor ferri sesquichloratis of the German Pharmacopœia); a dull green color is produced which immediately vanishes. Repeated additions of the same solution produce a repetition of the reaction. A quantitative test may be made by titration with a decinormal silver-nitrate solution. E. Meyer has found the average quantity between 0.66 and 0.3 per cent. in children, but it may rise to between 0.225 and 0.265 per cent. in adults.

Wolkow and Baumann claim that the reaction is due to the presence of a dioxyacid which they name homogentisinic acid and give the following test: Acidulate 250 c.c. of the urine with twelve-per-cent. sulphuric acid and add an equal quantity of ether. The mixture is thrice shaken and the ether is distilled off. The reddish-brown, syrupy residue is dissolved in water and the solution heated to nearly

boiling. A concentrated solution of lead acetate is added in the ratio of 30 c.c. to 250 c.c. On cooling acicular crystals of lead homogentisinate are formed. Although stained by accompanying pigments from the urine they are almost pure. Ogden recommends the use of basic instead of neutral lead acetate as it gives a more abundant yield of crystals.

Kirk attributed the alcapton reaction to the presence of uroleucic and uroxanthic acids, but Garrod has found both uroleucic and homogentisinic acids present in the same specimen.

Significance.—Alcaptonuria may occur at any time of life, from birth to old age, and its duration may be from a few hours to many years in any case. Several members of the same family may be simultaneously affected. Garrod finds that it occurs with especial frequency in the children of first cousins, but he has not found an instance of its transmission from one generation to another. Meyer attributes the condition to the influence of food, since he has found that the alcapton is increased by a meat diet. From the fact that the administration of tyrosin to the alcaptonuric patient increases the quantity eliminated, it has been inferred that tyrosin is responsible for the condition; and, since tyrosin is normally present in the intestine, it has been supposed that alcapton may arise from intestinal decomposition through the action of bacteria; but thus far, alcapton bodies have not been found in the intestine and the administration of intestinal antiseptics has had no influence upon the output through the kidneys. Alcaptonuria does not appear to be productive of harm.

Cryoscopy.

The name cryoscopy has been given to a method for determining the freezing point of urine. The method is employed chiefly to determine the functional capacity of the heart and kidneys. Although it was made use of by Bouchard as long ago as 1870 and more recently by Malassez, Hamburger, Koranyi, and others, it has received comparatively little attention. Credit is due to Dr. J. H. Huddleston, of New York, for having awakened an interest in the subject in this country, and it is chiefly to his article that the writer is indebted for the following description of the method.

The test is based upon Raoult's law of chemistry and Koranyi's theory of molecular interchange in the convoluted tubules of the kidney. Raoult's law holds that a molecule of any compound when dissolved in one hundred molecules of a liquid lowers the freezing point of the liquid by an amount which is nearly constant. A molecule of urea, and a molecule of sodium chloride, for example, should cause the same lowering of the freezing point. This reduction does not,

however, necessarily correspond to the increase of specific gravity, for the weight of different molecules is not the same. Blagden states that when two different substances are contained at the same time in the same solution the lowering of the freezing point is the sum of the reductions that would be caused by the two substances separately.

Koranyi's theory, briefly stated, is that the water which filters from the glomeruli contains in solution sodium chloride in amount sufficient to give to the solution the same osmotic tension as the blood plasma; and that as this solution passes through the convoluted tubules and loops of Henle, it returns to the blood a certain amount of sodium chloride, by osmosis, in exchange for an equal number of molecules of more complex substances. The rate of interchange is not the same under all circumstances. When, as under the influence of high arterial tension, the glomerular filtration is rapid and the urine flows rapidly through the tubules, the interchange is less, and *vice versa*. Impaired integrity of the epithelium lining the tubules also diminishes the molecular interchange.

If we let T represent the temperature of the freezing point of urine, C, a unit of volume, and V, the quantity of urine voided in twenty-four hours, CT will represent the number of molecules in a unit volume of urine, and CTV the total number of all molecules for twenty-four hours. If then T′ represents the freezing point of a solution containing the same amount of sodium chloride as the urine examined, $T - T' = T''$ will represent the lowering of the freezing point by the other solid ingredients and CT″V will equal their total quantity for twenty-four hours. And if W represents the weight in kilograms of the individual, CTV ÷ W equals the total number of molecules per kilogram in twenty-four hours and CT″V ÷ W = the excretion, per kilogram in twenty-four hours, of ingredients other than sodium chloride, or the complex molecular diuresis. In normal urine sodium chloride constitutes about three-twelfths of the average solid contents, urea and other organic compounds about seven-twelfths, and the sulphates, phosphates, and other metallic bases about two-twelfths.

Huddleston gives us the following example of the application of the method to a specimen of urine. The value of T was found to be −1.50°, of V, 1,500, and of W, 60. Since −0.613° has been determined to be the freezing point of a one-per-cent. solution of sodium chloride, the freezing point of a solution of any percentage must be Cl × −.613. In this specimen Cl was found to be 0.008 and the freezing point was therefore $0.8 \times -.0613 = -0.4904$, and $T'' = (T - T') = 1.50 - 49 = 1.01$. CTV ÷ W was $(C \times 150 \times 1{,}500) \div 60 = 3{,}750C$, and CT″V ÷ W = $(C \times 101 \times 1{,}500) \div 60 = 2{,}525C$.

The value of T, or the freezing point, varies normally, according to Lindemann, between −1.30° and −2.20°. Several ratios have been

especially studied by Koranyi. CTV ÷ W, representing the total molecular diuresis and varying with the increase or diminution of molecular interchange, was found to vary from 6,000 to 300. The rate of molecular exchange was found to be represented by the ratio of the total molecular diuresis to the complex molecular diuresis, or as (CTV ÷ W) : (CT′V ÷ W) = T ÷ T′, a ratio which normally lies between 1.49 and 1.69. The ratio of chlorine-containing molecules to the total molecular contents was found to be from 1.23 to 1.69. The amount of sodium chloride equivalent to the total solids of the urine varied from 30 to 50. The quantity in a given specimen must be determined by one of the volumetric methods.

The Method.—The apparatus necessary for the practice of cryoscopy consists of a double test tube, a stirrer, a freezing bath, and a thermometer. The test tube may be made by placing a flat-bottomed test-tube one inch in diameter and seven inches long within a slightly larger tube, preventing contact by placing rubber bands around the inner tube. The stirrer is made by bending a loop about five-eighths of an inch in diameter at a right angle on the end of a stiff wire of suitable length to serve as the handle. To the outer edge of the loop is fastened with fine wire a strip cut from the side of a goose feather. This must fit into the inner tube with sufficient accuracy to prevent the clinging of ice crystals to its sides. The thermometer, which is to be placed in the inner tube, must be capable of registering the hundredths, or, better, the thousandths, of a degree Centigrade. A lens is necessary to recognize these minute variations. An approximate test of the freezing point is now made by immersing the tube in a freezing mixture. A mixture of shaved ice and water is prepared in a felt-covered vessel and enough salt added to reduce the temperature of the slush to that of the approximated freezing point of the urine. The test tube is filled one-third full of the urine and placed in the freezing mixture until the thermometer falls to 0.3° or 0.4° below that of the freezing point just determined. The tube is then transferred to the mixture of ice and water and a minute crystal of ice is dropped into the urine in order to start the crystallization. The temperature rises slightly as the urine congeals, and in about one minute it may be read from the thermometer. In order to secure the slightest variation, it is necessary to tap the top of the thermometer with rapid but delicate blows. The stirrer must be kept in motion during the entire process.

Application.—Cryoscopy is employed as a test of function. It is not capable of detecting renal lesions so long as the kidneys functionate normally. Its chief application is to uncomplicated diseases of the heart or kidneys. Koranyi considers the examination of a case of heart disease incomplete without it. He asserts that passive hy-

peræmia of the kidneys is positively indicated by a high ratio of T ÷ Cl, and claims that glomerular and tubular nephritis may be differentiated by the method. Glomerulonephritis is to be inferred from a low value of TV ÷ W as compared with the normal value of T ÷ T'. The severity of the disease is revealed by the value of the ratios. If the value of T'V ÷ W is less than 500, a speedily fatal termination of the disease may be expected. Lindemann shows that the freezing point is raised in both acute and chronic nephritis.

When both heart and kidneys are diseased, the method is said to be of value for determining which is more at fault. If, in the presence of anasarca, the freezing point is below normal, the kidneys are not at fault; but if the freezing point is within the normal limit, these organs are somewhat affected, and seriously so if the freezing point is high. In the case of serous effusions, if the ratio T ÷ Cl is diminished, it signifies that the fluid is being absorbed; if increased, that it is becoming more abundant.

Bouchard has applied the method to the study of metabolism. In the course of the various nutritive processes, the albumin molecule is split up, the carbon being eliminated in parts by the lungs, intestines, and kidneys. Part of the sulphur and phosphorus is carried off in the form of sulphates and phosphates in the urine. In the process of breaking up, the molecule tends constantly toward the molecule of urea with atomic weight of 60. By-products are also formed, and when metabolism is incomplete, these by-products are more abundant than when they are complete. Their atomic weight is always more than that of urea, therefore above 60. By ascertaining the number of molecules in a twenty-four hours' specimen of urine and determining the average molecular weight, the completeness of metabolism may be estimated. The normal average molecular weight was determined by Bouchard to be from 62 to 68, but under abnormal circumstances, as in diseases of the lungs, liver, or kidneys, and in fever, it may reach 130.

Unfortunately for the method, Raoult's law is not universally correct. While it is exact for many organic substances, it does not hold good for the inorganic salts, acids, or bases. Corrections are therefore necessary at almost every step.

The Refraction Method.

A. Strubell, in the course of investigations on the density of urine and more particularly as a result of a study of the freezing point, has devised a new method by means of the refraction of light which he regards as so convenient, so rapid, and so exact that it is destined to occupy an important place in medicine as well as in physiological

chemistry. He regards it as much superior to cryoscopy. The method is based upon the physical law that when a ray of light passes from a thinner to a denser medium it is refracted toward the angle of incidence. The sine of the angle of incidence bears a constant relation to the sine of the angle of refraction, a ratio which represents the rapidity of the passage of the light through the two media. This ratio is called the exponent of refraction. If both these angles have been determined by means of hollow prisms filled with the fluid to be tested, the total angle of refraction can be determined.

The determination of the exponent of refraction has been heretofore a matter of difficulty in the examination of fluids, but the instrument of Abbé in a measure simplified the process and the more recently devised immersion refractometer of Pulfrich has practically removed all the difficulty. The instrument resembles a hand telescope with magnifying power of ten diameters, or it may be compared to a spectroscope. The prism is made of hard glass, having an index of refraction equal to 1.5, and an angle of refraction of 63°. The result is read from a scale on which the base line of water at 17.5° C. is 15. The ocular is provided with a micrometer screw and scale by which hundredths of a degree may be recognized. An accompanying table facilitates the computation. In making the test the instrument is immersed into the fluid to be tested. The temperature of the fluid is regulated by means of a water-bath of 17.5° C., in which glass cups are placed containing the fluid to be tested. The temperature must be carefully observed, as a slight variation vitiates the result of the refraction. The instrument is suspended from a metallic bar over the cups until the fluid has arrived at the desired temperature. The light is thrown from a mirror through a window in the side of the bath. A special bath is also provided for the testing of fluids which will not bear exposure to the air. The coefficient of refraction varies with the kind of light as well as with the temperature of the fluid, and it is disturbed if the specific volume is altered by external pressure.

In order to express the relation of density to the coefficient of refraction, Newton devised the formula $(n^2 - 1) \div d$. Gladstone and Dale have, however, found the formula $(n - 1) \div d$ equally accurate and more convenient. In it n represents the coefficient of refraction and d the density. From this formula, Strubell found that the refractive power of normal urine varies from 0.33261 to 0.33501, but that it seldom passes the limits of 0.333 and 0.334. In a range of specific gravity between 1.003 and 1.028, the exponent of refraction varied from 1.33436 to 1.33463, or from 17.9 to 45.0 on the scale of the Pulfrich instrument. The freezing point in the same range of density varied from −0.30° to −2.30° C. From this, Strubell concludes that it does not correspond to the variations of specific gravity,

or to the freezing point, and that it has nothing to do with the molecular volume of the substances held in solution. Comparing the results of the examination by the three methods of solutions of sugar, sodium phosphate, and sodium sulphate, he found that variations of one per cent. in their density caused variations in specific gravity amounting to from 0.0037 to 0.0039, and a difference in their freezing points of from $-0.011°$ to $-0.13°$ C., while the difference of refraction was 0.00142 for sugar, 0.00072 for sodium phosphate, and 0.00064 for sodium sulphate.

In a mixed solution like the urine, the author claims that the calculation is not so difficult as it at first appears. He employs a modification of the formula already given. If N represent the coefficient of refraction and D the density of the urine, n_1, n_2, n_3, the exponent of refraction of the several substances held in solution and d_1, d_2, d_3, their densities, then $(N - 1) \div D = ([n_1 - 1] \div d_1) + ([n_2 - 1] \div d_2) + ([n_3 - 1] \div d_3)$. And if by quantitative analysis the percentage of one ingredient of the solution, as sodium chloride, urea, or sugar, has been determined, it is possible to estimate the quantity of the other ingredients.

The applicability of the method has not been fully worked out. Although Strubell and Grober have employed it in the examination of the urine in most of its pathological conditions, the results are not yet sufficiently established to warrant positive statements in regard to them.

ADDISON'S DISEASE

AND

OTHER DISEASES OF THE ADRENAL BODIES.

BY

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In preparing a supplementary article on the subject of adrenal diseases, it is singularly interesting to find that large accessions to our knowledge have been made since my original article was composed. The advance already made respecting the anatomy and functions of the adrenal bodies since my student days is truly remarkable. Less than fifty years ago these organs were regarded as of no importance, and they had then neither an exact normal nor morbid anatomy, nor had their disorders a place in any nosology. Although there still remain large gaps in our knowledge respecting the exact normal functions of these glands, the progress already made, and the continued assiduous study, both of their natural and perverted functions, which is now directed to these by highly trained and competent observers give sure token that no long time is likely to elapse before we are made conversant with most of the difficult problems which still lie open for inquiry. Can we doubt that the writer of the article on this subject in a "Twenty-first Century Practice of Medicine" will be able to elucidate it with certainty and exactness?

In the course of the last few years some fresh researches have been made regarding the development of the adrenal bodies, their structure, and their functions. These are well set forth by Dr. Auld[1] in a work just published, with excellent illustrations. The main contentions of this observer indicate that in the medulla of the gland, at least, a substance is elaborated which is transmitted to the blood. "In the zona glomerulosa of the cortex the blood is purified by filtration, large numbers of red corpuscles undergoing disintegration in the gland cells of that layer. The blood in passing on to the medulla is subjected to further and more refined tests of purity, inasmuch as it is mixed with a secretion which contains an exceptionally powerful reducing agent. In how far toxic substances in the blood are decomposed and rendered

inert in the gland itself, or to what extent the secretion influences the body generally by passing into the general circulation requires evidence of a different kind. There seems, however, little reason to doubt that this secretion has directly or indirectly the control of normal color within certain limits, and that its arrest would form the principal factor in Addison's disease, in which the blood clots with difficulty, the red corpuscles refuse to form rouleaux, and the body becomes pigmented."

With respect to the active principle discovered by Oliver, Auld maintains that if there is an internal secretion essential to life, it must be carefully recognized that the active principle is only a constituent of that secretion, and not the entire secretion itself.

J. J. Abel has shown that the active principle is a base or poisonous alkaloid which he terms epinephrin ($C_{17}H_{15}NO_4$). According to Langlois the liver, the blood, and other organs rapidly destroy this substance. Auld conducted some careful experiments on extirpation of the glands. Removal of one gland appeared to have no noteworthy effects on the animals operated on, even after five months have elapsed. Removal of the second gland was followed by death in thirty-six hours, preceded by intense weakness and drowsiness, and in one case by convulsions. Some compensatory hypertrophy was noted in the remaining gland, and further, great hypertrophy of the thymus gland and of the spleen. These facts are of interest inasmuch as thymus extract is antagonistic, as regards its effects on blood pressure, to adrenal extract. The splenic enlargement suggests, as Dr. Auld believes, increased hæmolytic function. These observations have been corroborated by Boinet.

The latest researches point to the work of the adrenal glands being mainly carried on in their medullary portion where toxic bodies are reduced or destroyed, and fresh qualities are imparted to the blood through a specific secretion. This function cannot, apparently, be conducted elsewhere in the body. The rapidly fatal result which follows total extirpation of the glands appears to be due to a toxæmia, and we may fairly believe that the symptoms of Addison's disease are dependent on gradual autointoxication. Auld believes that the toxic agent in the blood is the physiological forerunner of the alkaloid produced in the adrenals. The latter is not found in the suprarenal venous blood.

Addison's Disease.

While accepting the modern view expressed in the above observations, it is not possible, I believe, to discard entirely the older ideas which regarded the implication of the great abdominal nerve centres in some cases as responsible for many of the clinical symptom of Ad-

dison's disease. It is too much the habit to throw over all the pre-existing theories in regard to a malady whenever a new view of it is promulgated. We have witnessed this in respect of the modern teachings about tuberculosis which would urge us to discard all the old views relating to scrofula, and direct our attention solely to the bacteriology of the matter. The laboratory is not, however, to overrule our clinical acumen, but is to be the handmaid of the practising physician. The younger physicians are now rather too apt to study in the physiological laboratory, and too little at the bedside, and we are in danger of losing our clinical instincts, and of neglecting our *patients* while we study *diseases*. In Addison's disease, as in all diseases, we have to observe carefully the clinical phenomena in each case, and to compare them subsequently with the precise revelations of the autopsy. In this way alone we shall gradually unravel the features of the disorder which are personal to each affected individual. A study of the personal factor is essential in every instance. Our modern text-books indicate only too forcibly the truth of these remarks, and the influence of our latest methods of investigation. We do not decry the latter, but more regard is called for to minute clinical observations in association with them.

The latest teaching regards Addison's disease as mainly due to an inadequate supply of adrenal secretion. It is not yet determined whether this deficiency induces a toxæmia or a general languor and apathy. Dr. Byrom Bramwell and M. Boinet, however, are disposed to regard nervous irritation and neuritis of the abdominal sympathetic fibres as a factor in association with the glandular inadequacy, and I am inclined to adopt their views as constituting the best exposition for the present of the pathogeny of this disorder. The purely nervous theory cannot of course apply to cases in which the only morbid change detected is atrophy of the glands.

The corpuscular richness of the blood and its hæmoglobin do not appear to be materially affected in Addison's disease.

Diagnosis.—The pigmentation in Addison's disease is to be distinguished from the condition recognized as acanthosis nigricans. In the latter the skin is rough and warty. The distribution of the pigment is not the same as in adrenal disease, and the buccal membrane is not involved in it. Cancerous disease is commonly associated with acanthosis nigricans.

In some cases of chronic Bright's disease, with contracted white kidneys, marked pigmentation of the skin sometimes occurs, and these have been erroneously diagnosed as instances of Addison's disease. The distribution of the pigment is, however, not such as is met with in the latter disease.

Treatment.—The results of treatment by suprarenal extract are still

sub judice. They are certainly not to be compared with those obtained by the employment of thyroid extract in cases of myxœdema. A dried extract of the sheep's gland is the form commonly administered, of which a grain is equivalent to fifteen of the gland tissue. This should be given thrice a day. The medullary portion alone contains any active principles. I have had satisfactory results in but one case in which I employed this plan of treatment. There was an increase in vigor, and freedom from most of the depressing symptoms which had not been markedly relieved by iron, strychnine, wine, and good diet. I lost sight of the patient, and have no means of knowing how far the benefit remained permanent. Dr. Bramwell is of opinion that this method of treatment is likely to be of use only when the adrenals are alone involved by the disease process, and when a spreading sclerotic change has not caught up the adjacent great nervous plexuses. It is mentioned by Oliver, of Newcastle-on-Tyne, and by Rolleston, that if this treatment is suspended, an increase of pigmentation takes place in the integuments. In any case, the treatment appears, if carefully carried out, to be devoid of harmful effects, and it would seem right to carry it on over long periods. Adrenal extract possesses a stimulating and tonic influence upon the muscular system, in addition to its action in raising the arterial blood pressure. Ralph Stockman found the treatment to be of no avail in two cases of tuberculous adrenal glands, but in one instance, probably due to atrophy of the organs, he noted great amelioration of symptoms and diminution of pigmentation, after treatment for two months with three to six sheep's capsules daily, taken raw, and he quotes another similar experience by Sansom.[2] It is not easy to understand why there should be a difference in respect of beneficial results in the two classes of cases. In the first place it can never be a matter of certainty whether there is fibrocaseous (tuberculous) disorganization of the adrenals, or a mere atrophy of them. In the former case the gross changes in the organs reduce their functions practically to the condition of atrophied ones in respect of the production of their important secretions, but, in addition, it may be expected that progressive sclerosing changes have spread in such cases to the adjacent nerve plexuses and gravely involved them.

The languor, nausea, and depression which occur in varying degree from time to time may sometimes be benefited, as I have found, by employing a few grains of asafetida in pill, and by tablets of erythrol nitrate containing half a grain given two or three times a day.

Cystic Adenoma of the Adrenal Body.

Dr. Bosanquet[1] records an instance of this, in which a tumor was found in the left hypochondrium, rounded and freely movable. It

occurred in a woman, aged fifty-six, who died of hæmatemesis from a malignant gastric ulcer. The cyst caused trifling discomfort. There was a similar smaller one in the other capsule which had remained small and suffered only mucoid or fatty change. The wall of the larger cyst was one-eighth of an inch in thickness, and its contents were turbid and resembled orange jelly. The wall was lined with cells resembling those of the gland. In the same communication Dr. Rolleston furnishes five other examples of adrenal cysts, four of which are recorded in the London Pathological Society Transactions, and one in Allbutt's "System of Medicine."

Adrenal Rests.

Aberrant fragments of adrenal tissue are not uncommonly met with adjacent to these organs, and under the capsule of the kidney, also in the liver and the broad ligament. They are very small, and seldom exceed the size of a pea. They consist usually of cortical material alone.

These adrenal rests may remain unchanged through life, or may sometimes after fifty years of age become enlarged and form tumors. Dr. B. H. Buxton[4] describes a case in which this occurred, and gives many references to other examples of this condition. These tumors appear to be of a sarcomatous nature. Mr. Arthur Eastwood[5] has lately studied this subject with much care, and discussed it most fully, especially with reference to the development of neoplasms in adrenal rests. He shows that the majority of these never undergo malignant alteration. His arguments are deserving of careful study.

Condition of the Adrenals in Cases of Pulmonary Tuberculosis.

M. Lancereaux[6] found in three hundred and twenty-eight autopsies of pulmonary phthisis that tubercles were present in the adrenals in five cases. These occur generally in the form of isolated caseous nodules, and are not productive of any symptoms.

Therapeutic Uses of Suprarenal Extracts.

Adrenalin, the active principle of the suprarenal glands, has been isolated in a pure form by Dr. Jokichi Takamine, who has published an account of his work. This substance has the approximate composition represented by the empirical formula $C_{15}H_{15}NO_3$, but its chemistry has not yet been completely worked out by its discoverer. It occurs in light, white, microscopic crystals, has a slightly bitter

taste, and leaves a numb feeling on the tongue where it has been applied. In dry form it is perfectly stable. It is soluble with difficulty in cold water but more readily in hot water, forming a slightly alkaline solution. It is easily soluble in acids and in alkali hydroxides, forming salts; such solutions readily oxidize on exposure to air. The physiological properties of adrenalin have been practically tested on dogs by Dr. E. M. Houghton, of Detroit, who finds that a fraction of one drop of aqueous solution of adrenalin or its salt, in the strength of 1 in 50,000, blanches the normal conjunctiva within one minute. It is a strong hæmostatic. The intravenous injection of adrenalin produces a powerful action upon the muscular system in general, but especially upon the muscular walls of the blood-vessels and of the heart, resulting in an enormous rise of blood pressure. The result of three intravenous injections of 1 c.c. of the solution of adrenalin chloride, 1 in 100,000, into a dog weighing 8 kgm., raised the blood pressure 30 mm. of mercury. This and other experiments indicate that adrenalin is over one thousand times stronger than the fresh glands. The therapeutic applications are already numerous. Generally speaking, when locally applied it forms a powerful astringent and hæmostatic; it may be used in various forms of inflammation and it is also a cardiac stimulant. It is said to be non-irritating, non-poisonous, non-cumulative, and without injurious properties. As an antidote it has been used with good results in opium poisoning, also in circulatory failure, in the prevention of collapse in anæsthesia, and in carrying out bloodless operations in the nose, eye, ear, and throat. It has also given good results in some cases of deafness, hay fever, nasal hemorrhage, and in various forms of heart disease.

I have employed adrenalin with marked effect in a case of persistent epistaxis arising in a man suffering from saturnine impregnation with arterial sclerosis, gout, and contracted kidneys, and in some other cases. It appears likely to have a wide sphere of employment.

John N. Langley [7] finds that adrenal extract causes a brief but active secretion of the salivary and lacrymal glands, and also increases the secretion of bile.[8]

Dr. Burnett,[9] aural surgeon to the Presbyterian Hospital, Philadelphia, reports an interesting case in which severe symptoms occurred from the use of a spray of adrenalin chloride, 1 to 1,000, which caused smarting and lacrymation, tinnitus aurium, cardiac excitement, and loss of smell and taste. The prescription was for a solution of 1 to 10,000. The patient was made very ill, with rigidity and nausea, burning head, and coldness of the extremities. Consciousness returned. Hypodermic injection of strychnine was useful in removing these untoward symptoms. It is clear that this agent requires care in

its administration. The fact that the adrenal medullary substance contains so powerful an agent is very noteworthy now when we reflect that those glands have for so long been considered inactive or unimportant in the animal economy.

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DIABETES MELLITUS.

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In 1895 I published an article on diabetes mellitus in the TWENTIETH CENTURY PRACTICE OF MEDICINE, Vol. II. At that time I endeavored to present in a concise but complete manner the most important points with respect to the pathology of this disease. The greatest weight, however, was laid upon the treatment of the disease which I sought to present in a more comprehensive and practical manner than had hitherto been done. That article was published simultaneously in Germany in the form of a monograph ("Die Zuckerkrankheit und ihre Behandlung," Berlin, Verlag von Aug. Hirschwald) which during the past year has reached its third edition. In this place I shall endeavor to communicate the advances which have been made in the pathology and treatment of diabetes between the first and third editions of my monograph. My experience with this disease has markedly increased since 1895, as in the interim I have treated over two thousand diabetics, nearly one-half of whom have been under careful clinical observation for several weeks in my private clinic and the city hospital of Frankfort-on-the-Main.

For the convenience of the reader I will consider the subject under the same subdivisions which were employed in the original article. Those chapters in which there is nothing new will, however, be omitted.

Definition.—Even to-day, if we would accurately designate the character of diabetes, we must be satisfied with a general description rather than a precise definition. Under diabetes mellitus we understand a disease in which the capability of the body to convert glucose is pathologically reduced. Endeavors have not been wanting to give prominence to the overproduction of sugar rather than to a deficient oxidation; nevertheless such endeavors, which have indeed been recently undertaken, are not to be considered advantageous. I emphasize that the disturbance principally concerns the conversion of glucose, for in diabetics the excretion of sugar is increased by only such carbohydrates as either directly or after previous change into glycogen

are converted into glucose by the secretions and ferments of the body. Recently Salkowski and others have shown that there are individuals who excrete the five-atomic carbohydrates (the so-called pentoses), in part independent of the food taken and in part after the ingestion of the pentoses present in the various vegetables. In those cases in which the pentosuria is dependent upon the food taken it does not deserve the least consideration. In those rare cases in which it appears independent of food there is present a peculiar, at present entirely unexplainable, anomaly of metabolism, but which clinically has no importance because it is unaccompanied by any pathological symptoms. Especially it has nothing to do with diabetic glycosuria. However, it is frequently confounded with such, because the most important reaction of glucose (the reduction of copper sulphate in an alkaline solution) is common to both glucose and pentose.

Origin of the Sugar.—The question whether, in addition to the sugar which is formed from carbohydrates, other sources of sugar exist, and which are especially operative in the sugar excretion in diabetes, has during the past few years been zealously investigated. Although E. Pfluger and his followers have recently emphasized their belief that there is no biological proof to show that glycogen and sugar ever originate from albumin, yet it is certain that such is the case. In opposition to the isolated opinions of E. Pfluger and his followers stand all chemists and physiologists who maintain that the origin of carbohydrates from albumin is a firmly established fact. In addition to the earlier well-known physiological facts it has recently been discovered that sugar can be derived from most albuminous bodies by the addition to the same, in the test tube, of acids (Kossel, Pavy, F. Müller, Blumenthal, and others). Whether in addition to this carbohydrate complex, which in the different albuminoids is variously active, other atom groups are present in the albumin molecule from which sugar can be derived, has been much discussed (Fr. Müller, Umber). No proof has been adduced that such is the case. This question to a certain degree depends upon the possibility as to whether or no the body is able to form sugar from fatty acids. Nine years ago, in my "Pathologie des Stoffwechsels," I pointed out that this was possible and probable. Since that time Th. Rumpf and my assistants (Rosenqvist, Mohr) have published cases which I believe support such a view. There are cases with an excessively high sugar excretion in which if one estimates how much sugar could be formed out of the carbohydrates of the nutrition and out of the oxidized albumin there remains, in addition, a considerable excess in the urine sugar which must arise from another source. I regard it as scarcely contestable that in such the fatty acids serve as a source of sugar. It must, however, be added that other authors (Naunyn, Fr. Müller, Umber, Gr. Lusk) deny the validity of such a

conclusion. New methods are required in order to settle this important theoretical and practical question.

Alimentary Glycosuria.—When the first edition of this work was published, the clinical researches with respect to alimentary glycosuria were very few. Since that time extensive observations have been conducted with respect to the frequency and intensity of the glycosuria which occurs in non-diabetics following the ingestion of large quantities of glucose, etc. The patients are given in the morning before breakfast, or about two hours thereafter, 100 gm. of glucose in water or tea ($\frac{1}{4}$ to $\frac{3}{10}$ litre) and the urine is examined six hours thereafter. Larger quantities of glucose should not be given because some sugar is found in the urine of many entirely healthy individuals following the single ingestion of 130–150 gm. If, however, this occurs after the ingestion of 100 gm. it is certain that the assimilation of glucose is subnormal. This is often observed in neurasthenic patients, namely, in those in whom the disease has arisen from traumatism (so-called "traumatic neuroses"). In them the demonstration of sugar in the urine, thus produced, is of great importance in the perplexing differentiation between genuine neurasthenics and impostors. Furthermore, alimentary glycosuria can often be easily produced in Graves' disease, in obesity, and in chronic alcoholism during and immediately after the delirium. According to the observations of my former assistant, J. Strauss, glycosuria can be produced in alcoholics by the administration of large quantities of starch (*glycosuria ex amylo*). This is a very important discovery because it shows the intimate relation which exists between experimental glycosuria *e saccharo* and genuine diabetic glycosuria. According to the earlier conceptions these conditions had nothing to do with each other. Finally it is to be mentioned that, aside from diabetes mellitus, acute febrile conditions, such as pneumonia, erysipelas, etc., are more prone to alimentary glycosuria and show it in a more marked degree than all other diseases (von Noorden and H. Poll). Of the two factors here concerned, the elevation of temperature and the intoxication, the latter appears to be chiefly responsible for the reduction of the assimilating power (P. F. Richter). Although numerous researches have been conducted with respect to the relation of alimentary glycosuria to liver diseases, little that is positive has been gained therefrom. The view of H. Strauss that liver diseases more often show an alimentary lævulosuria than glycosuria has to my knowledge not been satisfactorily confirmed.

Experimental Diabetes.—Leaving out of consideration the transient glycosuria following Claude Bernard's puncture and other nerve injuries, toxic phloridzin diabetes and diabetes after extirpation of the pancreas are alone to be considered in this place. In regard to both of these conditions the researches of the past few years have confirmed

many known facts, but little that is new and of importance has been added.

The glycosuria following phloridzin poisoning must be regarded as nephritic in origin—that is, the kidneys under the influence of the poison lose the power to prevent the sugar from passing out of the blood. Endeavors to nullify this view have not been convincing. Recently efforts have been made to employ phloridzin glycosuria for diagnostic purposes, in that diseased kidneys after inoculations of phloridzin excrete less sugar than healthy kidneys. By catheterization of the ureters the secretion of both kidneys has been separately obtained, and it has been possible to ascertain whether one or both kidneys were diseased. However, the diagnostic value of the employment of phloridzin in renal surgery must be further demonstrated before a decision with respect to its importance can be made.

In regard to the diabetes which occurs after extirpation of the pancreas little has been gained by the researches of recent years. Even to-day, twelve years after its discovery, we must be satisfied with the insufficient explanation that the pancreas by means of an "internal secretion" produces a substance which passes into the blood and is indispensable for normal carbohydrate metabolism. If this substance as the result of extirpation, destruction, or disease of the pancreas ceases to pass into the blood, the sugar molecule is not broken up and is excreted in the urine. There is a tendency by some to maintain that in every case of diabetes in man the function of the pancreas is pathologically perverted (a reduction or absence of the internal secretion), even in those cases in which gross and microscopical examination of the pancreas with the employment of hitherto available methods shows no pathological changes. These endeavors to unify the unsolved etiology of diabetes are misleading, and it must not be forgotten that this conception at present is merely an hypothesis and that the cases of human diabetes are a minority in which at autopsy pathological lesions of the pancreas are found.

The more caution should be preserved since recently F. Blum has demonstrated the presence of a substance in the suprarenal glands, the subcutaneous injection of which gives rise to a marked glycosuria. The little that is at present known in regard to this suprarenal diabetes, which perhaps stands in a certain relation with the condition described as "diabète bronzé," is sufficient to show that the pancreas is not the only organ concerned in carbohydrate metabolism.

The Glycosuria of Diabetics.

The old subdivision of M. Traube, which divides diabetic glycosuria into two forms, a severe and a mild, has with some modifications been retained. This is proper because such a subdivision is of clinical im-

portance and furnishes both prognostic and therapeutic data. On the other hand, the conception of Seegen, according to whom severe and mild glycosuria are to be regarded as two distinct pathological conditions showing different perversions of the metabolic processes, has been relegated more and more to the background. Indeed this view, vigorously contested by Külz and myself, is now entirely abandoned. I can cite at least one hundred cases in which an original mild glycosuria has been gradually converted into the severe form.

The extraordinarily pronounced modifications which mark the course of a severe glycosuria have rendered necessary the establishment of a middle form. This was first proposed by Naunyn. Here are to be included cases in which the urine cannot be made sugar-free by the mere withdrawal of carbohydrates, but in which this can be accomplished by the simultaneous reduction in albuminous food and a corresponding reduction in the albuminoid metabolism. It is not easy accurately to define the limits of this middle form. I have described the following forms which have been generally accepted by others:

Glycosuria is to be regarded as mild when it yields to the simple withdrawal of carbohydrates without it being necessary at the same time to reduce the amount of albuminous food below the quantity usually partaken of by diabetics. By the usual quantity I understand an amount of albuminous food which is accompanied by an excretion in the urine of 8–15 gm. of nitrogen daily (in children about 18–20 gm.).

Glycosuria is moderately severe when for its disappearance is necessary in addition to the withdrawal of carbohydrates a sufficient reduction of albuminous food, so that less than 18 gm. but more than 10 gm. is excreted in the urine (in children from 13–7 gm. of nitrogen).

Glycosuria is to be regarded as severe when it is entirely or only partially relieved by the withdrawal of carbohydrates and marked reduction in albuminous food, so that less than 10 gm. of nitrogen are excreted daily in the urine (in children less than 7 gm.).

The middle form of glycosuria is to be regarded as a transitional stage in that it frequently passes into the severe or the mild form. According to my experience it most frequently results from those cases of mild glycosuria which are neglected or treated in an incompetent dietetic manner. In such, by the employment of a careful therapy and rigorous regimen, it is often possible to bring about a return of the disease to the mild form and to maintain it there.

Directions for the Estimation of the Intensity of a Glycosuria.—In every case of diabetes one should immediately endeavor to estimate carefully the intensity of the glycosuria. These estimations must from time to time be repeated. In order to obtain comparative values I always begin with a so-called "test diet." This is composed of (1) a carbohydrate-

free diet, the "chief diet," and (2) a carbohydrate-containing diet, the "accessory diet." For the latter I always select white bread. On the first day I order 100 gm., divided between breakfast and lunch. Later, according to circumstances, the quantity of bread is increased or diminished, or the same quantity is distributed differently throughout the day. In addition, observations are made with respect to the effect of other carbohydrates such as milk-sugar, fruit-sugar, etc. Coincident with the sugar estimations the quantities of acetone, oxybutyric acid, nitrogen, and ammonia excreted should be estimated so far as it is deemed necessary. At the end of this test ("tolerance estimation"), which consumes from eight to ten days, I have determined most accurately the *status quo*, and with the greatest certainty can outline a dietetic regimen which is suitable for the present and individual necessities of the patient. If this test is repeated from time to time one gains a complete survey of the entire course of the diabetes, and at any time one can estimate the influence which the diet, medication, waters, etc., have exerted, so that it can be easily determined in what manner, if any, the treatment should be altered. These tests naturally require much experience and perfect accessory appliances. They can be carried out with dispensary patients, but when it is possible I always advise the patient to remain in hospital at least during the fundamental test.

Scheme for the First Day of the Test Diet.

Breakfast. Chief diet: 200 c.c. of coffee or tea with one or two tablespoonfuls of thick cream, 100 to 150 gm. of cold meat (ham, etc.); butter.

Accessory diet: 50 gm. of white bread.

Noonday Meal. Chief diet: beaten egg or omelette without flour, with spinach, cauliflower, asparagus, etc. Meat with salad or cucumbers and with sauce made without flour. Cheese and butter. Coffee with two tablespoonfuls of thick cream. One or two glasses of wine.

Accessory diet: 50 gm. of white bread.

During the Afternoon. Tea with two tablespoonfuls of thick cream. One egg. No accessory diet.

Supper. Chief diet: Meat broth with egg or bone marrow. Fish with butter or butter sauce. One or two chops with vegetables (green beans, lettuce, cabbage, cauliflower, asparagus, spinach, tomatoes, cucumbers, but no roots, or shelled peas or beans). Cheese, caviar, sardines, crabs. One to three glasses of wine. No accessory diet.

Example of a test in a diabetic forty-eight years of age, with mild glycosuria. I designate only the accessory diet; the chief diet varied daily in order to be diversified, but was always free from carbohydrates.

		Sugar in urine.	Acetone in urine.
First	day twice 50 gm. bread	40.9 gm.	0.92 gm.
Second	" four times 25 "	37.1 "	.89 "
Third	" three " 25 "	29.8 "	
Fourth	" twice 25 "	21.5 "	.82 "
Fifth	" twice one-third litre milk	25.6 "	
Sixth	" twice 170 gm. apple.....	17.8 "	.74 "
Seventh	" once 25 " bread.....	13.2 "	
Eighth	" no carbohydrates.....	6.8 "	.79 "
Ninth	" " "	2.1 "	
Tenth	" " "	.....	.74 "
Eleventh	" " "	....	
Twelfth	" " "	.....	.65 "

After six weeks' treatment, during the first part of which a rigid diet was enforced but during the latter part of which a small addition of bread was allowed, the following results were obtained in the second test:

		Sugar in urine.	Acetone in urine.
First	day once 25 gm. bread	.....	0.41 gm.
Second	" twice 25 "	.....	.82 "
Third	" three times 25 "	.....	.....
Fourth	" twice one-third litre milk.....	.....	.28 gm.
Fifth	" twice 170 gm. apple	.....	.22 "
Sixth	" three times 25 "	.....	.19 "
Seventh	" four " 25 "	8.9 gm.	.17 "
Eighth	" twice " 50 "	4.9 "	.....
Ninth	" " " 25 "	.....	.19 gm.

At a subsequent test after a year's interval the patient bore 100 gm. of bread divided into bi-daily and quarto-daily doses without the excretion of any sugar. When 125 gm. of bread was given daily, traces of sugar appeared in the urine.

I will not here further consider the laws upon which the intensity of diabetic glycosuria is dependent. It is well known how the various carbohydrates (starch, lactose, levulose, saccharose, inulin, etc.), the amount of albuminous food, exercise, psychical disturbances, intestinal and stomach indigestion, intercurrent diseases, etc., influence the glycosuria. Nothing new has been added thereto in recent years. I would state that recently it has been especially shown how frequently acute infectious diseases occurring during the course of a diabetes increase the intensity of the same (febrile angina, influenza, pneumonia, erysipelas). There have been several cases described by my assistant, L. Mohr, in which an originally mild diabetes, immediately following such diseases, passed into the severe form. In all probability the infection had left behind a permanent injury of the parenchyma of the pancreatic gland.

Acetone.—Among the acetones oxybutyric acid, acetic acid, and acetone are included. It is now generally regarded that oxybutyric acid

is the mother substance. It is probably a normal intermediate metabolic product which by the healthy body is converted into higher oxidized products. The quantity of acetones produced in the healthy body is so small, or their conversion is so complete that only traces of the end-product (acetone) which escape destruction appear in the urine. Abnormal nutritive conditions increase the quantity of acetones and consequently the excretion of acetic acid and oxybutyric acid. A true pathological increase, however, occurs only in diabetes mellitus.

Practically the following is important: If there arise in the body large quantities of oxybutyric acid, this acid is excreted in the urine in substance (that is in sodium or ammonium salts). Furthermore there are present large quantities of acetic acid and acetone, and the latter, being very volatile, is also present in the expired air ("fruit breath").

If there arise only moderate quantities of oxybutyric acid in the body, this substance does not appear in the urine or is present in traces only, but a portion of its oxidized derivatives is excreted as acetic acid and acetone.

If there arise in the body only small quantities of oxybutyric acid then neither oxybutyric nor acetic acid appears in the urine. Nevertheless normally a portion of the acetone arising from these acids is excreted. The quantity of acetone excreted in the urine in twenty-four hours is, in non-diabetics upon the usual diet, a few centigrams. This is increased by an exclusive meat or fat diet to about 1 dcgm.

Formerly it was supposed that the acetones were derived from the albuminates, and there is no doubt but that they may arise from such since they have been produced from albuminous bodies *in vitro* (Blumenthal and Neuberg, A. Orgler). Nevertheless it is probable that the greatest quantity of acetones excreted in severe cases of diabetes originates from the fatty acids. In general in diabetes the larger quantities of acetones are present in the urine in those cases in which the ability of the body to convert and oxidize carbohydrates is markedly reduced; yet it is certain that other factors are operative, since of several diabetics in whom the carbohydrate-converting power is practically identical some showed larger quantities of the acetones in the urine than did others.

The appearance of the acetones signifies that the blood and tissues are overladen with acids (acidosis). From such a condition, if it is permanent and increases, or other factors are present which reduce the vitality of the patient, there may develop the specific diabetic intoxication, diabetic coma. For this reason the excretion of the acetones is of prognostic value. So long as the quantity of the acetones excreted is very small, only a few decigrams, there is nothing to fear. If,

however, the daily quantity increases from 1 to 2 gm. and reaches 3 to 5 gm. or more, and in spite of careful treatment this quantity cannot be reduced, the probability of an unfavorable turn must be prognosticated. A very convenient way of reckoning the acidosis is to be found in the estimation of the ammonia, provided the patient is not taking large quantities of alkalies (sodium bicarbonate, etc.). A. Magnus-Levy has shown that the daily excretion of about 2 gm. of ammonia corresponds to about 6 gm. of oxybutyric acid, 5 gm. of NH_3 to about 20 gm., and 8 gm. of NH_3 to about 36 or 40 gm. of this acid.

Chemistry of the Blood.

Bremer has drawn attention to the fact that the blood of diabetics, if spread upon a cover glass in a thin layer and heated to 135° C., stains much less intensely than normal blood with certain aniline dyes (Congo red, methylene blue, methylene green, etc.). This has been confirmed as regards the majority of the mild and severe cases of diabetes which have been examined. However, the reaction is not obtained with certainty in all cases of diabetes, and furthermore it is also present in other pathological conditions (Lépine). This robs the reaction of its diagnostic value, but it does not detract from its curiosity. It has not yet been definitely determined why the red blood cells refuse to stain with their normal intensity. The increased amount of sugar in the blood is not the cause; the intensity of the reaction does not correspond with the intensity of the glycosuria. It is present in diabetics who for a long time previously have ceased to excrete glucose and in whom certainly there is no hyperglykæmia.

Complications of Diabetes.

Among the various organic disturbances which may accompany diabetes I mention only disturbances of the heart and digestion because recently these have been extensively studied. With respect to other pathological lesions much new detail has been added during the last few years, but no important advances have been made.

Disturbances of the Heart—Heart Weakness.—Simple atrophy of the heart muscle is the pathological lesion which is often the basis of the heart weakness observed in diabetics; with this may be combined fatty degeneration and dilatation. The atrophied heart is most frequently seen in greatly debilitated patients. Frequently the heart weakness is dependent upon local causes (sclerosis of the coronary arteries) and the resulting malnutrition of the heart muscle. In old persons, especially men, the influence of diabetes upon the heart is not easily studied. In such arteriosclerosis, adiposity, gout, and contracted kidneys are frequent complications, and in addition extreme cardiac

irritation and overstrain, resulting from excessive work or the misuse of alcohol and tobacco, are frequently present so that one is at a loss to determine what proportion of the cardiac alterations are due exclusively to the diabetic condition. I would especially emphasize this in opposition to the views of Th. Schott, who much too narrowly limits the relation of true heart diseases to diabetes. Young diabetics offer the best material for research along this line. At autopsies upon such one almost never finds complicating pathological changes in other organs which could cause heart lesions, and the heart itself is simply atrophied, such an atrophy merely corresponding to the general muscular atrophy present. Precisely in conformity with this a large number of diabetic children, young adults, and persons in middle life, who are free from complications which could influence the heart, show the evidences of a weak heart—marked excitability of the heart on the one hand and quick tiring of the heart on the other. These are appearances entirely comparable to the condition of the heart which is encountered in severe chlorosis and anæmia. Similarly as in anæmia we find palpitation of the heart even to tachycardia after severe bodily exercise, psychical disturbances, excessive use of tobacco and alcohol, overeating, etc., dyspnœa after quick walking or climbing, rapid changes in the character and frequency of the pulse, often irregularity, complaints of oppression in the chest in the region of the heart, etc.

I would not be understood to say that all diabetics of such a category show these signs of a weak heart. In many they are not present even in the advanced stages of the disease; in others, however, they are early present and play an important part in the symptomatology of diabetes. In general heart weakness and muscular weakness are parallel with each other, but this is not always the case; for example, one often meets individuals who show powerful muscular development but who possess a heart exceptionally inadequate for the requirements of the body. The history will generally show that the heart has been overstrained.

I will give an illustration: Miss Edith L., from New Orleans, showed in March, 1899, sugar in the urine. On a rigorous diet the urine contained 1 to 1.5 per cent. of glucose. Since the observation was made that a marked reduction in the excretion of sugar followed bodily exercise, a journey to Switzerland was recommended. This was especially agreeable to the young lady and her relatives because the patient had previously undertaken mountain climbing with good results. On the way to Switzerland she consulted me. Although the twenty-one-year-old patient gave the impression of a muscular and healthy individual in spite of the presence of the sugar in the urine, I counselled her against mountain climbing and advised other meas-

ures. However, my advice was not followed. The patient went to Switzerland and ascended several high mountains. I, therefore, was not astonished when she returned to me, six weeks later, with extraordinarily marked cardiac weakness. She was now both a diabetic and a cardiac patient, although the other muscles of the body were in as good condition as previously and so remained. The heart, however, remained permanently weak.

That in young and old diabetics the cardiac weakness is immediately dependent upon the diabetes, is seen in many cases by the striking therapeutic result of a careful dietetic treatment under which in unison with the general muscular improvement the heart regains, as a rule, its normal capability. After extensive experience I regard it as an error to treat cases of primary diabetic heart weakness essentially as cardiac cases. The apparent results obtained thereby would be at the most transitory. Of course it is to be understood that with dietetic treatment suitable methods for increasing the heart tone should be combined (gymnastics, etc.), but great care should be taken and the limit of cardiac power should not be exceeded. I have seen no benefit in diabetes from the employment of the carbonic-acid baths so widely recommended in cardiac weakness of organic origin. Indeed in young individuals these are especially disadvantageous, as they increase the irritability of the heart and add to the heart strain. It is naturally otherwise if the heart weakness is of other origin (for example, valvular) and merely complicates the diabetes. Here under certain conditions such measures are both useful and necessary and the balneological treatment of the cardiac weakness may precede or follow energetic dietetic measures.

Among my patients, whom I have observed for a long time in the hospital or private clinic, I have seen 34 (4.4 per cent.) in whom cardiac weakness, unaccompanied by severe organic lesions of the circulatory apparatus, played a pronounced part in the clinical picture and necessitated active therapeutic treatment. Therein are naturally not included those cases of cardiac weakness which first developed *sub finem vitæ*. In other cases the signs of heart weakness are never clinically prominent until quite suddenly the heart becomes paralyzed and the patient dies under the picture of "heart failure." This I have observed five times among one hundred and forty deaths of diabetics. Instantaneous heart failure has nothing to do with diabetic coma. The catastrophe usually occurs after unwonted strains, as for example after mountain climbing, fatiguing journeys, or psychical disturbances.

Valvular lesions are often met with as accidental complications arising from a previous polyarthritis. When compensation fails the results of the valvular lesions become clinically manifest and assume

prominence. I have often observed that diabetics with valvular lesions show no œdema even under conditions in which anasarca is regularly present in non-diabetics. Schott says that in diabetic cardiac diseases the administration of digitalis is to be avoided. In this I cannot concur. Indeed I have seen as good results from the use of digitalis in diabetics, if indeed not in the above-described primary diabetic cardiac weakness, yet certainly in true cardiac diseases (valvular lesions, myocarditis, etc.), as in non-diabetics.

Cardiac Neuroses.—Attacks of palpitation and stenocardia, without anatomical heart lesions, are frequently present in diabetes, in nervous individuals more often than in the phlegmatic. They arise either in consequence of the previous condition of the nervous system or are causally connected with the diabetes in that this disease lays the foundation for hysterical, neurasthenic, and hypochondriacal manifestations.

Although it is often difficult to establish a direct connection between the diabetes and such marked cardiac neuroses, nevertheless the frequency of such a concurrence is astonishing. Not less than eighty-one of my clinically observed patients (10.5 per cent.) showed the presence of such functional disturbances, especially tachycardia and mild stenocardia, without demonstrable anatomical lesions of the heart, blood-vessels, and kidneys. If the patients had been non-diabetics I would have without hesitation ascribed the cardiac appearances to neurasthenic or hysterical causes, and there is no reason why this conception should be altered merely because diabetes was present. The course as a rule was favorable, much more favorable than in non-diabetics in so far that regulation of the diet, methodical muscular exercise, and the improvement in the general condition brought about by psychical rest, produced quick recovery. I do not agree with those who hold that in such cases a rigorous diet should be avoided.

If we pass by the severe form of angina pectoris, which in the presence of anatomical lesions of the coronary arteries is often met with in diabetes, the cardiac neuroses of diabetics are very often associated with the excessive use of alcohol and tobacco. Diabetics are much less resistant to tobacco than healthy individuals. This is seen in the frequent occurrence of the cardiac neuroses as well as of disturbances of vision. I have often observed that patients with severe cardiac neuroses could be entirely freed from these unpleasant symptoms by the withdrawal of tobacco and the institution of a rigorous dietetic regimen.

Steatorrhœa.—In a few cases of diabetes the fæces are of a grayish-white color and of an extremely disagreeable odor. Careful examination shows that such fæces contain an enormous amount of fat and nitrogenous substances (steatorrhœa and azotorrhœa). The passages greatly resemble those met with in severe cases of icterus, but signs

of retention of bile are absent. It may be conceived that in such cases either the pancreatic juice passes into the intestine in an insufficient amount or the pancreas in connection with the non-production of its internal secretion has also lost the ability to produce its specific digestive ferment. In such cases we find in the fæces about sixty per cent. of the ingested fat and about twenty-five per cent. of the ingested nitrogenous substances. Such patients are not in a condition to assimilate the carbohydrates and to utilize the albuminoids and fats. For this reason they emaciate rapidly and experience marked muscular weakness. For many years I have endeavored to find an efficient medication for this condition. Especially have I tested all the various pancreatin preparations which I could obtain since I made the discovery that the administration of scraped pancreatic gland (sheep or calf), when fresh and uncooked, was followed by a transient improvement. After many unsatisfactory tests I obtained from a manufacturer in Aachen a pancreatin which in a dose of 1 gm. three or four times daily markedly improved the absorption of fat and albuminous material. "Pancreon" (a combination of pancreatin and tannic acid) gives better results than pancreatin. However, larger doses of this preparation are necessary (5 to 6 gm. daily). The details of the action of these two preparations are to be found in an article by Salomon in the *Berliner klinische Wochenschrift*, 1902, No. 3.

Treatment.

The principles of the treatment of diabetes have not been altered during the past few years and to-day dietetic treatment is chiefly to be relied upon, reinforced by various measures (hydrotherapy, climatotherapy, massage, gymnastics, etc.) which are directed toward the improvement of the general condition. I will not enter into a consideration of this auxiliary treatment since there is nothing new to be said with respect to it. Recently an attempt has been made to bring into prominence the medicinal treatment of diabetes, but such endeavors have met with little encouragement from scientific physicians. Usually with the various medicines advertised a rigorous dietetic regimen is prescribed; thus if the sugar is reduced this is to be ascribed to such a regimen and not to the medication. I have recently tested a number of these remedies and regard them all as valueless. They are not only worthless but they weaken the patient's faith in the benefits of dietetic treatment.

Although no new principles have been added to the dietetic treatment, yet it has been improved and more firmly established by the advances in the knowledge of metabolism and the chemistry of food than was the case ten years ago. It has been especially learned that

the diet should be more carefully regulated to the individual needs than was formerly done and than is even now generally appreciated. It will indeed not be indiscreet if I ascribe to myself the service of having especially emphasized the importance of an individual dietetic treatment which has been more and more indorsed by physicians and also by patients. The principles of this form of treatment are given in the toleration-tests which have been above described. On account of the necessity of the same and because of the results thereby produced, the periodical hospital treatment of diabetes has come into vogue (in hospitals, sanatoria, or private clinics). While ten years ago diabetics, and then only severe cases, were very rarely treated in this manner, the hospitals which have recently been erected for the special use of diabetics are, in Germany at least, very frequently sought. I alone have treated during the past year more than one hundred diabetics in my private clinic for this disease. The hospital treatment in no way makes superfluous the careful home treatment of diabetes and the use of water cures; it merely supplements them. The hospital treatment is principally used for the establishment of the tolerance and for the institution of a rigorous dietetic cure. Its duration is usually but three or four weeks. Such measures can be only imperfectly carried out at home and then with great disadvantage to the patients.

I cannot give the details of such treatment here, but the important points for the dietetic treatment may be stated as follows:

In all cases of diabetes previous to the beginning of the special dietetic treatment, it should be definitely ascertained by the above-mentioned tests how much carbohydrates the patient bears without the excretion of sugar. This should be determined in all cases, whether of a mild, moderate, or severe form of glycosuria.

In *mild cases*, especially in the beginning, the diet should be so arranged that the ingestion of carbohydrates remains below the toleration limit, and so that consequently no sugar is excreted. It is the greatest error to be satisfied with a marked reduction in the amount of sugar excreted even if it sinks to very low limits (below one or one-half per cent.). If one is satisfied with such a result, it is certain that the tolerance will be gradually decreased. Only when sugar has been absent from the urine many weeks and months is it probable that the tolerance has been significantly increased. When such is the case it is often possible gradually to cure the disease, a view which must be specially emphasized in opposition to the earlier regarded incurability of diabetes.

The permanent absence of sugar from the urine can be practically reached only when the tolerance exceeds 75 to 80 gm. of white bread. If the ingestion of less bread caused sugar excretion, the diet would have to be more rigorous than could be continued for a long period.

I recommend for patients with mild glycosuria (a tolerance of more than 75 to 80 gm. of bread) a beginning with a two-weeks' treatment by an absolutely rigorous diet. This is then gradually modified by the addition of 10 gm. of bread each day until the tolerance is increased about two-thirds. When this is attained the treatment is maintained for several weeks, but in each week one day of an absolutely rigorous diet is prescribed. In all such cases frequent treatment at Carlsbad is of advantage.

Cases of Moderate Intensity.—When the tolerance is less than 80 gm. of bread I recommend the following: The patient begins with a four- to six-week cure by an absolutely rigorous diet, which is to be repeated twice or three times during the year for a period of two to three weeks (the original cure is best taken in a hospital). In the intervals between the cures 80 gm. of bread daily or its equivalent (see table at the end of this section) is allowed. However, during the intervals single days should be selected upon which the rigorous diet is to be observed. In these cases it is wise to restrict in a certain degree the amount of albuminoids ingested; this should be controlled by estimations of the amount of urea in the urine, which should not exceed 25 gm. per day. Among cases of this kind one often meets with those in which the urine gives the reaction with chloride of iron. This reaction as well as the quantity of acetones and ammonia very often increases in the first days of a rigorous diet. If such an increase lasts more than four or five days, the continuation of the diet is not absolutely negatived, but great care is necessary. Repeated careful observations must be made and the diet in the mean time discontinued if the general condition is unfavorably influenced. Very often under a less rigorous diet the excretion of the acetones will diminish. In such cases the diet cure, if of long duration, is better carried on in a hospital than at home.

In cases of *severe glycosuria* it is necessary to separate those in which life may be prolonged for a considerable period from those in which such is not possible. Such a separation is, however, not easy. There are no criteria and much personal experience is necessary for the correct decision of this question.

In hopeless cases matters are very simple. A rigorous diet is useless. It serves only to annoy the patient. The marked permanent restriction of carbohydrates is not advisable. On the average about 100 gm. of white bread or its equivalent should be given daily. This is sufficient to allow the patient a wide latitude in diet. Great importance is to be laid on the abundant administration of fat and alcohol. Alcohol is not interdicted even if albumin appears in the urine in addition to the sugar.

With respect to patients in whom a considerable prolongation of

life is anticipated, I would say that I have known diabetics who have suffered for more than ten years with the severe form of glycosuria, and in whom the daily quantity of carbohydrates has corresponded as a rule to 100 gm. of white bread or its equivalent. If such, however, is continued without interruption, disagreeable complications will arise which are dependent upon the hyperglykæmia (neuralgias, disturbances of vision, pruritus, gangrene, etc.). For this reason the usual allowance of 100 gm. of white bread daily should, twice a year, be interrupted by a four to six weeks' period of a rigorous diet. These periods markedly contribute to the building up of the tissues and the entire body. They serve to protect the patient in a great measure from the above-mentioned complications of a degenerative character. I regard it as a very great error to maintain that patients with severe glycosuria bear a rigorous diet badly. Numerous experiences have convinced me that the opposite is true with respect to a certain very large group of cases. This group of cases includes those in which a satisfactory general condition is present, and most of those in which the severe glycosuria has originally gradually developed from the mild form. However, the rigorous diet in severe glycosuria needs careful watching, and at least in the beginning of the cure the patients should, if at all possible, be treated in the hospital.

It is of the greatest importance to recommend in all cases of severe glycosuria the continuous use of alkalies. I usually give a mixture of equal parts of sodium bicarbonate and citrate in doses of 5 gm. before breakfast and 5 gm. on retiring in one-fourth of a litre of hot water. During the day I give in addition 5 gm. of calcium carbonate divided into two portions. The alkalies facilitate the excretion of the acids and prevent the dangerous acidity of the blood.

If appearances of acid intoxication present themselves and signs of diabetic coma, the alkalies should be still further increased and the diet during such a period consist exclusively of milk. After much experience I regard the milk diet—with the exception perhaps of very light cases of glycosuria—as harmful to diabetics, but in threatened coma its temporary use is often of great utility. In actual diabetic coma I never neglect the intravenous injection of a three-per-cent. soda solution, as recommended by Naunyn, but I have never seen more than temporary improvement obtained thereby.

Diet Tables.

In my former article I gave diet tables which were quite different from those hitherto in use. I had the pleasure of observing that they were very well received. Especially have the so-called equivalence tables been generally accepted. The marked advances

in our knowledge of the chemistry of the food have necessitated many changes, and I now present a copy of these tables in the corrected form.

TABLE I.

This table contains the varieties of food of which every diabetic may partake.

Fresh Meat. All the muscular portions of the ox, cow, calf, swine, sheep, deer, tame and wild birds,—baked, fried, or roasted, with egg sauce, with butter, with mayonnaise, and other sauces made without flour; warm or cold.

Internal Portions of Animals. Tongue, heart, lung, brain, calf's sweetbread, kidney, bone-marrow, liver of calves, game, and birds (paté de foie gras) to 100 gm. (weighed when prepared).

External Portions of Animals. Feet, ears, snout, tail of all edible animals.

Preserved Meat. Dried meat, smoked meat, smoked and salted tongue, pickled meat, ham, bacon, smoked goose breast, American canned meat, Australian corned beef, sausage containing no bread, head cheese.

N.B.—It is to be noted that pickled meats of all kinds as offered for sale are usually prepared by the addition of sugar to the pickling fluids. Care should therefore be taken to ascertain that such meats are sugar-free. In large pieces of meat, for example ham, this caution is unnecessary.

Meat Peptones of all kinds, jellies and spices prepared from calves' feet or from pure gelatin; somatose, nutrose, eucasin, tropon, plasmon, etc.

Fresh Fish. All fresh fish from salt or fresh water, boiled, baked, or grilled. If the fish is baked with breadcrumb this must be removed before eating. Accessories: All sauces prepared without flour, preferably abundant butter and lemon juice.

Preserved Fish. Dried fish, salted, smoked fish as halibut, shell fish, codfish, herring, mackerel, flounders, sturgeon, salmon, sprat, eels, etc.; pickled herring, sardines à l'huile, mackerel à l'huile, sardelles, anchovies, tunny fish.

Fish Derivatives. Caviar, cod-liver oil.

Crustaceans. Oysters, clams, mussels, lobsters, crabs, etc.

Prepared Meat and Fish Sauces. The well-known English sauces and those prepared in a similar manner; beefsteak, Harvey, Worcester, anchovy, lobster, shrimps, India Soy, China Soy, etc., may be used in the usual small quantities if not especially interdicted.

Eggs raw or prepared as desired, but without flour.

Fat. Animal or vegetable fat, as butter, lard drippings, suet,

goose fat, olive oil, sesame oil, ordinary salad oil, oleomargarine, cacao butter.

Cream. Good rich cream, sweet as well as sour, may be added to food and also drunk—if not forbidden for other reasons—in quantities of two-tenths of a litre per day. The cook should make abundant use of cream since its employment in the preparation of meat, fish, vegetables, and eggs renders the addition of flour unnecessary.

Cheese. Every variety of cheese, especially the so-called cream cheese, in daily quantities of 50 gm.

Pastry. Flour-free almond pastry (prepared by O. Rademann, Frankfort-on-Main, and Callard & Co., London, 65 Regent Street).

Fresh Vegetables. Salads: Head salad, frizzled and smooth endives, Romaine, field salad, watercress, tomatoes, dandelion.

Garnishing. Parsley, dill, pistachio, minced cabbage, leek, garlic, celery leaves.

Green Vegetables. Cucumbers, tomatoes, green beans (young), vegetable marrow.

Bulbs. Onions, turnips (when green), radishes, horseradish.

Stalks. White and green asparagus, rape stalks, hop tops, English celery, chickory, young rhubarb stalks.

Blossoms. Cauliflower, broccoli, Brussels sprouts, artichokes.

Mushrooms. Fresh mushrooms, stone mushrooms, egg mushrooms, morels, truffles in the usual quantity.

Fruits. Of all the fruits are allowed only whortleberries, unripe gooseberries, and young raspberries when cooked with saccharin or crystallose instead of sugar. These may be partaken of in any desired quantity. The sugar-free fruits for diabetics prepared by O. Rademann in Frankfort-on-Main are allowable.

Preserved Vegetables. Preserved asparagus, haricots, string beans, salted cucumbers, mixed pickles, vinegar cucumbers, peppered cucumbers, sauerkraut, preserved olives, mushrooms, and other of the above permitted vegetables when preserved.

Spices. Salt, white and black pepper, Cayenne pepper, peppers, curry, cinnamon, cloves, musk, English and German mustard, saffron, anis, caraway seed, laurel, capers, vinegar, lemon juice.

Soups. Meat broths made from any kind of meat or meat extract, with the addition of green vegetables, eggs, pieces of meat, bone-marrow, fish, crustaceans, liver, Parmesan cheese, and other substances which are mentioned in this table.

Desserts. From eggs, cream, almonds, lemon, gelatin in the preparation of which saccharin or crystallose has been employed instead of sugar.

Drinks. All sorts of artificial and carbonated waters. Good cog-

nac, rum, brandy, Scotch whiskey, rye whiskey, cherry wine, plum brandy, etc.

Sparingly of sugar-tested wine; Muscatelle, Rhine wine, maple wine, Bordeaux, Burgundy, sugar-free champagne in the quantity ordered by the physician.

Tea and coffee with cream but without sugar, in place of which saccharin or crystallose may be used in any desired quantity.

Cocoa. Fifteen grams of Rademann's diabetic cocoa or Van Hövel's saccharin chocolate.

Lemonade, effervescent seltzer water with lemon juice and sweetened with saccharin, crystallose, or pure glycerin; lævulose when specially permitted.

TABLE II.

This table contains those varieties of food which are of high nutritious value and of especial value to diabetics.

Fat. Butter, lard, suet, goose fat, game fat, oils of all kinds, cod-liver oil.

Milk Preparations. Sweet and sour cream of good quality, cheese of all kinds, especially the different varieties of cream cheese.

Meats. The nutritive value of meats increases with the proportion of fat which they contain. Fat pork and mutton have a higher nutritive value than lean beef and veal.

Sausage and Smoked Meats. Those prepared from pork excel in nutritive value. In mixed meat preparations those are the most nutritious which contain the largest proportion of pork.

Fish. Among these fresh- and salt-water eels, salmon, and mackerel possess the greatest nutritive value.

Eggs. All eggs are of high nutritive value, especially the yolk, which is about five times as nutritious as a like quantity of the white.

Caviar is also to be included among the eggs.

TABLE III.

This table contains those varieties of food which if they are not specially interdicted may be partaken of in the small quantities here indicated. If, however, the diet is rigorous they are not to be allowed.

Vegetables (cooked without flour or sugar). Dried white beans, dried yellow or green peas, chervil turnips—one teaspoonful.

White cabbage turnips, bog turnips, carrots, celery bulbs, black root, green fresh or preserved peas, large wax beans, as vegetables or salad—two tablespoonfuls.

Radish. A small quantity of radishes of about 50 gm. weight,

Nuts. Six walnuts or ten hazelnuts or eight almonds or eight pecan nuts.

Fresh Fruits. Apples, pears, apricots, peaches about 50 gm. in weight, raspberries, whortleberries, a heaping tablespoonful; blackberries, two tablespoonfuls.

Cooked Fruits (without sugar and sweetened with saccharin or crystallose). Plums, apples, pears, apricots, peaches, cherries, a heaping teaspoonful; raspberries, gooseberries, two heaping tablespoonfuls.

Dried Fruits (apples, prunes, peaches). Cooked after soaking in water, a heaping tablespoonful.

Milk. One-tenth of a litre.

Lævulose-chocolate. Stollwerck's, 15 gm.

Cocoa. Rademann's (without the addition of sugar), 15 gm.

TABLE IV.

This group includes foods which are rich in carbohydrates. In a rigorous diet they are interdicted, but otherwise they may be allowed in certain quantity. This quantity varies in different cases and at different periods, and should be prescribed by the physician. Since white bread is the standard, the amounts of the various substances are given in terms of white bread, that is, the quantity of such a substance which corresponds to a given quantity of white bread. For this reason the table is called

TABLE OF WHITE BREAD EQUIVALENTS.

White bread.	10 gm.	15 gm.	20 gm.	30 gm.	40 gm.	50 gm.
Corresponds to:						
Rye bread, Hardtack, Seidl's gluten bread, Rhenish black bread, Graham bread, Aleuronat zwieback, Pumpernickel	12	18	24	36	48	60
Gluten zwieback (Seidl's), Gluten bread (Fromm), Porter bread (Gericke)	13	20	26	39	52	65
Aleuronat (Günther)	15	22	30	45	60	75
Porter-zwieback (Gericke)	12	18	24	36	48	60
Gluten-zwieback (Fromm)	12	18	24	36	48	60
Rademann's pastry (Frankfort-o.-M.)—						
Diabetic bread, " cakes, " zwieback	15	22	30	45	60	75
" white bread, " black bread	20	30	40	60	80	100
" sticks	30	45	60	90	120	150
Almond bread	300	450	600	....	....	....

White bread.	10 gm.	15 gm.	20 gm.	30 gm.	40 gm.	50 gm.
Corresponds to:						
Cocoa (pure)	20	30	40	60	80	100
Acorn cocoa (Stollwerck)	12	18	24	36	48	60
Saccharin chocolate (Hövel)	32	48	64	....	....	....
Lævulose chocolate (Stollwerck)	10	15	20	30	40	50
Diabetic cocoa (Rademann)	25	37	50	....	....	....
Natural meals—						
Wheat, rye, barley, oats, corn, millet, buckwheat	7.5	11	15	22	30	37
Beans, peas	10	15	20	30	40	50
Starch of—						
Potatoes, wheat, tapioca, rice, sago, corn	7	11	14	21	28	35
Flour products—						
Nudels, maccaroni	7.5	11	15	22	30	37
Cereals—						
Oats	10	15	20	30	40	50
Barley, rice	9	18	18	27	36	45
Hulled fruits—						
Peas, beans (dried)	12	18	24	36	48	60
Peas, beans, hog beans (fresh)	20	30	40	60	80	100
Bulbs—						
Potatoes	30	45	60	90	120	150
Celery bulbs	50	75	100	150	....	....
Turnips	21	30	42	60	80	100
Fresh fruits—						
Ox-heart cherries, mulberries	50	75	100	150	200	250
Cherries, apples, pears, bananas	60	90	120	180	240	300
Plums, gooseberries	75	110	150	225	300	375
Strawberries	85	120	170	250	340	425
Apricots, peaches	100	150	200	300	400	
Raspberries, whortleberries	120	180	240	360	480	
Round plums, queen plums, blackberries	150	225	300	450	600	
Oranges, melons	160	240	320	480	640	
Fruits of various kinds in their own juice (prepared without sugar). The juice is to be avoided.	150	225	300	450	750	
Desugarized fruits	250	375	500			
Milk, etc.—						
Full milk	135	200	270	400	540	
Sour milk	150	225	300	450	600	
Kefir	240	360	480	720	960	
Diabetes milk (Gärtner)	500	750	1,000	1,500	2,000	
Cream (ordinary good)	150	225	300	450	600	
Sterilized Swiss cream	200	300	400	600	800	
Beers—						
Clear Rhenish beer	200	300	400	600	800	
Pilsener	170	250	340	500	680	
Bavarian	150	225	300	450	600	
Grätzer, Lichtenheiner	250	375	500	750	1,000	

ILLUSTRATION OF THE USE OF TABLE IV.

We divide the food:

a. Into a carbohydrate free portion: "the chief diet."

b. Into a carbohydrate portion: "the accessory diet." For example—100 gm. of white bread:

1. First breakfast. Chief diet: Moderately strong tea or coffee, cold meat; one egg. Accessory diet: 40 gm. Rademann's diabetic white bread = 20 gm. white bread.
2. Second breakfast. Chief diet: two eggs in any form.
3. Midday meal. Chief diet: Soup with egg, meat with vegetables or salad, cheese, butter. Accessory diet: 75 gm. potatoes = 25 gm. white bread; 125 gm. strawberries = 15 gm. white bread.
4. Afternoon meal. Accessory diet: 0.3 litre of thick Swiss cream = 15 gm. white bread.
5. Evening meal. Chief diet: Warm or cold meats with vegetables or salad, cheese, butter. Accessory diet: One oatmeal cake of 20 gm. of oats or 40 gm. Rademann's diabetic bread = 25 gm. white bread. Total equals 100 gm. white bread.

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RHEUMATISM.

BY

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The Infectious Theory of Rheumatism.

THE tendency of recent writers on the subject of the pathogenesis of rheumatic fever is to discard the old view as to the nature of the rheumatic poison—the view which regarded it as a chemical product circulating in the blood—and to adopt that which I advocated in my article on rheumatism in Vol. II. of the TWENTIETH CENTURY PRACTICE OF MEDICINE, that it is a minute organism.

Since that article was written various writers have advanced the view that acute rheumatism is an infectious disease which may be communicated to man and the lower animals. Newsholme[1] believes that it is allied in nature to typhoid fever, scarlet fever, diphtheria, and influenza, and gives various statistics which he thinks lend support to this view. He adduces no evidence, however, that the malady is ever communicated from the sick to the healthy. The absence of such evidence, and his inability to bring any forward, he explains by the fact that "the contagium is buried in the affected joints." Future research may possibly lend weight to this view. At present it is quite unsupported by evidence. Dr. Newsholme's researches are very interesting, but it is impossible not to be struck by the looseness of his phraseology. In the absence of direct evidence of communicability the use of the word "contagium," as applied to the rheumatic poison, has no justification. Equal laxity is shown in the use of the term epidemic which he uses to explain circumstances to which the word endemic more fitly applies. Though Dr. Newsholme argues against the malarial theory of rheumatism his facts really lend support to the view that rheumatic fever is allied to malarial fever, and they are readily explained on the supposition that, like malarial fever, it is endemic (not epidemic) in certain localities, is more prevalent at certain seasons, and is more common some years than it is in others.

Various observers, notably Achalme,[2] Thiraloix,[3] Bettencourt,[4] Poynter, and Paine[5] have described and figured a minute organism

—a bacillus or a diplococcus—which they believed to be the rheumatic poison, and which, injected into the circulation of rabbits, produced the symptoms of rheumatic fever. The inferences which have been drawn from these observations are to be received with much caution, and that for several reasons.

First, so far as we know, rabbits are not subject to rheumatic fever, and, therefore, not susceptible to the action of the poison of that disease.

Second, they readily become the subjects of septicæmia.

Third, the symptoms of septicæmia in rabbits are fever, inflammation of the membranes of the heart, and effusion into the joints. These are the symptoms presented by the rabbits experimented on by the authors quoted. But as they are also the symptoms of rheumatic fever as it occurs in man, the inference was drawn that these rabbits had rheumatic fever, and that the cause of this was the bacillus or the diplococcus which was injected into their systems. Fever, heart troubles, and effusion into the joints are the symptoms of septicæmia as it occurs in man too. The specialty of rabbits is the readiness with which septicæmia is induced in them by what seem to be very innocent injections. It seems probable, on these grounds, that all the rabbits which were supposed to have rheumatic fever, to which they are not susceptible, were really suffering from septicæmia, to which they are very susceptible.

That the poison of rheumatic fever is a minute organism which enters the system from without is the opinion which I hold and advocate. That this poison will one day be recognized, as the plasmodium malariæ has been, I thoroughly believe. Meantime direct evidence of its recognition is wanting. This want has proved no obstacle in the way of treating the disease and arresting the action of its poison. The question as to whether that poison is a bacillus or a diplococcus, whether it is long or short, or straight or bent, a rod or a dot, is interesting to the biologist and bacteriologist, but to the clinical observer, to the physician, and to the sufferer from rheumatic fever it is a matter of no practical importance. The important thing is to recognize, first, that the disease never is communicated from the sick to the healthy, and, second, that the salicyl compounds exercise on its poison an even more destructive action than quinine does on the *plasmodium malariæ*, and arrest the course and symptoms of rheumatic fever with a corresponding rapidity. The exact action by which they bring about this result is a matter on which there is room for some difference of opinion. I have already, in Vol. II., given expression to my belief that they act by destroying the rheumatic poison—killing the germ of the disease. But until it has been demonstrated that this germ is allied to the poisons of the specific fevers rather than to that

of malarial fever let us not call it a contagium, for to do so is to beg the question and to introduce much possible error. The natural history of the disease to which it gives rise is, as explained in my article in Vol. II., more like that of malaria than that of the continued fevers, while the action of the salicyl compounds in full dose on the course of rheumatic fever and the rapidity with which they put an end to the disease, bear so close a resemblance to the action of full doses of quinine in ague that the analogy forces itself on our attention. In the whole range of practical medicine we know of only two instances in which an acute febrile disease, which if left to itself would run on indefinitely, has its course speedily arrested by a drug: these are the action of quinine in ague, and the action of salicin in rheumatic fever. That fact dominates the whole question of the pathogenesis of these two diseases, and separates them by a sharp line of demarcation from all others.

One great practical difficulty there is in investigating the bacteriology of rheumatic fever. As soon as the nature of the malady is recognized we are bound at once to administer large and frequent doses of salicin or salicylate of sodium. The risk of endocarditis or pericarditis or even of hyperpyrexia is so great, to say nothing of the pain of the arthritis, that no conscientious physician would make one hour of unnecessary delay. If the salicyl compounds act by destroying the rheumatic poison, as I believe they do, their administration puts a stop to the chance of a satisfactory investigation of its bacteriology.

In ague one may make observations on the blood before and after the administration of the quinine, and can note the fact of the destructive effects of the quinine on the organism found during the pyrexial stage. In rheumatic fever one dare not do this.

A definite form of fever is not the only effect produced on the system by malaria. With or without a previous attack of fever, a man exposed to malaria may lose health, become pale, listless, unfit for sustained effort, and more or less anæmic. There may be no fever, no apparent disturbance of the function of any organ. The condition has been fitly described as malarial or paludal cachexia. It is the result of the general enfeebling action of residence in a malarial district, and is not recovered from till that district is left. It is a condition of chronic malarial poisoning. Besides this general cachexia, malaria may cause localized disturbances of particular organs or tissues. Many cases of neuritis and of neuralgia are of malarial origin; so too are certain forms of derangement of liver, spleen, and bowel. Medicinal treatment may benefit these, as it may benefit malarial cachexia, but recovery is much aided and hastened by removal from the malarial district.

The rheumatic poison likewise produces on the system other effects besides a definite form of fever, and other local lesions than those noted in rheumatic fever. Anæmia is a sequence of acute rheumatism; indeed, there is scarcely any acute disease in which this result is produced so rapidly and to so marked an extent as it is in acute rheumatism, when the disease is allowed to run its natural course. There is too some evidence to show that children of rheumatic parentage are more apt than others to become anæmic.[6] Such a condition is fitly described as rheumatic cachexia.

Anomalous Forms of Rheumatism.

The age of liability to the regular arthritic form of rheumatism, polyarthritis rheumatica, is from fifteen to fifty. It is within these years that rheumatism, as it commonly manifests itself, chiefly occurs. It does so because from fifteen to fifty is the period of functional activity of those textures (the fibrous structures of the large joints) which are specially affected, and because it is only during their period of functional activity that these textures are a suitable nidus for the rheumatic poison. But the rheumatic constitution does not begin at fifteen and end at fifty. It exists both before and after these limits. It is often an inheritance which exists from birth. It essentially consists in the presence somewhere in the textures of the body of a something which makes these textures a suitable nidus for the development of the rheumatic poison. From fifteen to fifty this something exists in the muscles and fibrous textures of the large joints. Before fifteen and after fifty it exists not in the joints but in other textures, as is evidenced by the fact that the joints do not suffer. Hence it is that anomalous forms of rheumatism occur chiefly before and after the age of liability to the regular arthritic form of the disease.

It is the peculiarity of the seat of the rheumatic nidus, and the extent to which that nidus exists in the system, that determine the nature and the severity of a rheumatic attack. In ordinary rheumatic fever it exists to a large extent in the muscles and fibrous textures of the large joints; because of its existence there, the rheumatic poison is developed in, and acts on, these textures; because of its abundance the poison is developed largely, and produces a correspondingly marked inflammation.

Anomalous forms of rheumatism occur chiefly before fifteen and after fifty; but the disease manifests itself in different ways at each period. The rheumatism of childhood manifests itself by symptoms and lesions peculiar to that age. That of old age has also its own special features.

THE RHEUMATISM OF CHILDHOOD.

The textures which suffer in the rheumatism of childhood are to a great extent those which we find suffer in ordinary rheumatic fever—the motor apparatus, the fibrous textures, the heart, and the skin; only they do not suffer in quite the same way.

In connection with the *motor apparatus* we may refer to the frequency with which chorea, which is a functional disturbance of the motor centres, occurs in children of rheumatic constitution.

The skin is much affected in rheumatic fever, acid perspirations being almost essential to the diagnosis. It has long been a matter of clinical observation that various forms of erythema have a special association with rheumatism. Many years ago Begbie drew attention to the frequent occurrence of erythema nodosum in rheumatic subjects. The following are the chief conclusions to which he came: "(1) The skin affection is most prevalent in, if not confined to, the young, and those under thirty, the chief subjects of the rheumatic diathesis and of rheumatic fever. (2) It is associated frequently with rheumatic fever, coexisting or alternating with it. (3) It is often complicated with those internal disorders with which rheumatism is allied, particularly with pleurisy and pneumonia. It has also been noticed in connection with endocarditis, or other cardiac disease."

More recently Dr. Stephen Mackenzie [1] has brought forward a mass of valuable evidence which seems amply to warrant his conclusions. "(1) That erythema nodosum is frequently associated with definitely rheumatic symptoms, *e.g.*, arthritis, sour sweats, sore throat, etc. (2) That heart disease (endocarditis) may arise during an attack of erythema nodosum, both in cases in which arthritis is present, and in cases in which there is no affection of the joints. (3) That these conclusions justify the inference that erythema nodosum is frequently, if not generally, an expression of rheumatism, even when no other definitely rheumatic symptoms are present."

The rheumatic poison may in exceptional cases cause pains, febrile disturbance, and even acid sweats, without giving rise to any affection of the joints. Such cases occur more often in girls than in boys. The symptoms are slight fever, the temperature being generally about 100°, aching of the limbs, some tenderness on pressure at the seat of aching, and not uncommonly an eruption of erythema (nodosum, marginatum, or papulatum) on the arms or legs or both. The following case is illustrative of this condition:

A girl, aged 15, had always had good health, except for occasional attacks of tonsillitis. The family history is rheumatic. I was asked to see her, after she had been "out of sorts" for two days, suffering also from pains in the back, shoulders, and legs, because "spots" had

come out on her legs and pained her a good deal. She had well-marked erythema nodosum on both legs; there was tenderness of the muscles of the shoulder and of the thighs; the tongue was furred, the pulse 84, the temperature 100.2°; there was slight acid perspiration; there were no joint pains; the tongue was furred, and the bowels were constipated. She was ordered a calomel purge, and fifteen grains of salicin every two hours; was put upon a light diet, and told to remain in bed.

On the following day the temperature was normal, and she felt much better. The nodules of erythema were not so red and not so painful. On the next day she had still further improved, and the nodules were bluish in color and fading. Recovery followed speedily.

This case was one of subacute rheumatism in which the poison affected only the muscles and the skin. Such cases are not uncommon in girls. The fibrous structures of their large joints have not yet reached the stage of development and vigor at which they become a suitable nidus for the rheumatic poison. But the rheumatic constitution is there, and it is the muscles and skin which present the conditions necessary for the reproduction of the poison. Hence we have a rheumatic attack without any joint affection. Such cases may be fitly compared to those of the eruptive fevers in which the special lesion is not developed—variola sine variolis, morbilli sine morbillis. Their rheumatic nature is demonstrated by the occasional occurrence of cases presenting exactly the same symptoms, but in which one or more joints are the seat of true rheumatic inflammation.

Pharyngitis or *tonsillitis* is common in connection with rheumatic attacks, and not unfrequently occurs in rheumatic subjects as an isolated lesion. It is most common in children.

Subcutaneous nodules constitute another manifestation of rheumatism in childhood; they are more common among girls than among boys. These are round or ovoid nodules situated in some of the fasciæ or along tendons. Their size varies from that of a pinhead to that of a small filbert. Their most common seat is about the elbow or hand, though they are encountered quite frequently elsewhere. At first they may be slightly tender on pressure, but generally they are painless. They may last from a few days to several weeks. My experience leads me to agree with Cheadle in regarding them as essentially rheumatic, and never due to any other cause. These nodules bear to the rheumatism of childhood the same relation that arthritis bears to that of adult life. What constitutes the rheumatic constitution, and makes an individual susceptible to rheumatism, is the presence in the fibrous textures of the motor apparatus of something which makes them a suitable nidus for the rheumatic poison. It is when these fibrous textures have reached their full development, and in that part of them which is most highly developed and possesses most functional activity

—the fibrous textures of the large joints—that this peculiar something is most abundant. It is in these textures, therefore, that the rheumatic poison is reproduced, and on them that it acts. In childhood while the fibrous textures of the joints are as yet imperfectly developed, and are not called upon to do active duty, the rheumatic poison finds its nidus rather in the fasciæ and in the tendons. The rheumatic poison, therefore, is apt to cause in children not arthritis, but inflammation of a patchy character in the fasciæ and tendons. The inflammation is not acute, and it occurs in textures of low vitality and little vascularity, but it is sufficient to cause proliferation of the cellular elements and consequent thickening of these textures at the point of irritation. The result is the development of subcutaneous nodules.

Pleurisy and pneumonia are often of rheumatic origin, and may occur, especially the former, as an isolated lesion or in association with arthritis, erythema, or other manifestation of rheumatism. They occur both in childhood and in adult life, but more often in the young than in those of more mature years.

Endocarditis.—In ordinary articular rheumatism heart complications are more apt to occur in young subjects than in those of more mature years, and the younger the sufferer the greater is the danger of the heart becoming involved. It need not, therefore, surprise us to find that endocarditis and pericarditis are not uncommonly noted as occurring along with the irregular manifestations of the disease which present themselves before puberty. Heart troubles are especially apt to arise in connection with the occurrence of subcutaneous nodules. Cheadle, who has devoted much attention to the subject, regards "the eruption of large nodules as almost equivalent to a sentence of death. They mean persistent cardiac disease, generally uncontrollable, and marching almost infallibly to a fatal ending."

They are unquestionably of grave import, not because of any serious effects which they themselves produce, but because they are all but invariably accompanied by progressive disease of the heart. Of the twenty-seven cases observed and reported on by Barlow and Warner[8] all had heart disease. These nodules are, indeed, only one indication of a general rheumatic cachexia in which the fibrous textures of the heart are as apt to be affected as are the fibrous structures of the fasciæ and tendons in which the nodules occur. In acute articular rheumatism occurring before the age of twenty the heart is often affected and the earlier in life a rheumatic attack occurs the more likely is the heart to suffer. The heart trouble, which is an all but invariable accompaniment of the subcutaneous nodules, probably exists before these are developed—the first incidence of the rheumatic poison being on the heart. All the structures of the heart are liable to suffer, and the younger the patient the more extensive is the involve-

ment apt to be. Hence it is that the heart troubles noted in connection with subcutaneous nodules are often more severe and fatal than those noted in connection with arthritis. It is not the nodules, but the age at which they occur that makes the difference, and that causes the large mortality noted in these cases. Of Barlow's and Warner's twenty-seven cases eight proved fatal—an enormous percentage.

For this greater mortality of rheumatic inflammation of the heart in children there are two reasons: First, the organ is more excitable, beats more quickly, is therefore more affected by the disturbance which inflammation causes, and is in consequence less amenable to treatment. Rest is what is wanted; at no age is this attainable, but we are further from it in children than in adults, for their hearts are naturally more excitable. Second, the muscular substance is more apt to be affected in children than in adults. In the adult an endocarditis is more apt to remain an endocarditis, and a pericarditis a pericarditis; but in early life the inflammation spreads from the fibrous structures of the rings and valves to the pericardium and to the muscular substance, producing a general carditis which at that age is with difficulty recovered from. It is this tendency to the occurrence of myocarditis which makes these cases so fatal. The heart trouble begins in the fibrous rings and valves, causing there proliferation of the cellular elements and consequent thickening. It is exactly the same change which is noted in the rheumatic endocarditis of the adult. It is well known that in the adult the mischief at times extends to the pericardium and to the muscular substance. The same thing occurs in the child, only the process is a more active one, and the tendency to spread more marked.

In the child as in the adult there are many cases in which the cardiac trouble is slight, and in which complete recovery takes place. It is not unlikely that some of the cardiac murmurs noted in certain cases of chorea are really due to a temporary thickening of a portion of the fibrous textures of the heart.

The fibrous structure of the rings is proportionately more apt to be thickened in children than is the corresponding texture in the valve; hence stenosis is more common as a result of rheumatism in children than it is in adults. Indeed, I regard it as not improbable that many cases of mitral stenosis in which the lesion is supposed to be congenital are really the result of rheumatic endocarditis occurring in childhood or even in infancy.

The important point to be borne in mind is that the description of the rheumatic state as it occurs in the adult does not apply to the same state as it manifests itself in childhood. In the adult, arthritis and acid sweats form the characteristic feature of the attack; in children

these are replaced by erythema and subcutaneous nodules. In children, too, the heart is more liable to suffer than it is in the adult, and very commonly the first incidence of the rheumatic trouble is on the heart.

But the heart is subject to rheumatic inflammation before the joints. Indeed, of all the structures of the body, the fibrous structures of the heart are those which give the earliest evidence of being subject to rheumatism. To the frequent occurrence of endocarditis in connection with erythema and subcutaneous nodules reference has just been made. It often occurs independently of these, as an isolated lesion, and when it is associated with them it is probable that the endocarditis existed first. The period of greatest liability to rheumatic arthritis is between the ages of fifteen and thirty-five years; that of greatest liability to rheumatic endocarditis is between ten and twenty-five years.

It is of importance that we should recognize that though acute articular rheumatism, polyarthritis rheumatica, does not usually occur before the age of fifteen, the rheumatic tendency exists from early childhood, and the structures which are most apt to be affected by the rheumatic poison, should it gain entrance to the system of a child of rheumatic constitution, are the fibrous structures of the heart. It is because the period of functional activity of the fibrous structures of the joints is from fifteen to fifty, that it is chiefly within these limits of age that those textures are a suitable nidus for the rheumatic poison. It is because the period of functional activity of the fibrous structures of the heart begins so much earlier that they earlier are a suitable nidus for the rheumatic poison, and at an earlier age become subject to rheumatism.

Rheumatic Cachexia.—As there is a malarial cachexia from which some people, resident in a malarial district, are more liable to suffer from than others, so there is a rheumatic cachexia from which children of rheumatic constitution are apt to suffer without the development of joint disturbance. The symptoms by which it declares itself are anæmia, chorea, erythema, subcutaneous nodules, endocarditis, pericarditis, myocarditis, pleurisy, one or two or more of these. The gravity of the condition depends much on the extent to which the heart is affected. Unfortunately that organ is in not a few cases hopelessly damaged before the patient comes under notice.

Hyperpyrexia does not occur in the rheumatism of childhood. The muscles and heat-forming apparatus are not so disturbed as in the more acute rheumatic attacks of the adult. Heat inhibition is not stimulated so as to keep down excessive formation; there is, therefore, no chance of this function being exhausted or paralyzed. The circumstances which combine to produce such a result in the adult do not exist in the child.

Treatment.—The treatment of these anomalous forms of rheumatism is not different from that which should be adopted in the arthritic form of the disease. The tendency to heart complication is so great that salicylate of sodium should be used with great caution. Salicin, given in frequent dose, and some alkali are the suitable remedies. Absolute rest in bed, and light nourishing diet should be insisted upon until it is certain that the danger to the heart no longer exists.

The Rheumatism of Old Age.

In advanced life rheumatism assumes an anomalous form, inasmuch as it does not take the form of arthritis.

The structures which chiefly suffer are the large muscles, their aponeurotic attachments, their sheaths, and their tendons. The larger nerves and their sheaths, especially the brachial plexus and the sciatic —the nerves, that is, which supply the chief structures affected in articular rheumatism—are often the seat of a low form of rheumatic disturbance. Rheumatism affecting these structures is never acute in character, and does not give rise to fever. The pain is generally dull and aching, and is increased by movement and by pressure over its seat.

Just as the special rheumatic manifestations of childhood may also occur in early adult life, so these more senile manifestations of the disease may occur in middle life, especially in women. They are most common, however, after the age of fifty. At whatever time they occur they are apt to be obstinate.

Treatment.—The chief remedies are salicin, salicylate of sodium, quinine, and iodide of potassium. With this general treatment there may often fitly be combined massage, rubbing, and such treatment as is got at various medicinal springs.

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GOUT.

BY

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SINCE the appearance of the article on Gout by Dr. Lyman, in Vol. II. of this series, many investigations have been made and much has been written on the subject, but comparatively little has been added to the sum of knowledge regarding the disease. One, and perhaps the most important, certainly the most interesting, result of the study of gout in this country has been the demonstration of the fact that the disease is by no means so rare in America as was once supposed. In a paper read at the annual meeting of the American Medical Association in 1902, Fletcher showed by a comparison of the statistics of the Johns Hopkins Hospital, Baltimore, and St. Bartholomew's Hospital, London, that gout—at least in hospital patients—is barely one-third more frequent in England than it is in the United States, the ratio being very nearly 4 to 3.

Etiology and Pathology.—In spite of all the work of numerous investigators, many of the problems relating to this subject are still shrouded in mystery. Researches of various workers continually yield conflicting results.

Fletcher attributes the increasing number of cases of gout in hospital patients to lead poisoning and the influence of malt liquors.

Loewi has contributed some interesting observations concerning the metabolism of the nucleins. He has demonstrated that nuclein is formed in the body not only from nuclein itself but also from other substances. The greater part of the nucleins in the intestine is absorbed *in toto*. A part, however, is broken up into phosphoric acid which is thrown out in the fæces, while the nitrogen is retained and absorbed. In some cases an increase of the nuclein in-put caused a retention of its elements. Gouty subjects were noticed to have an increased retention of nitrogen and phosphoric acid between attacks. No end-products of nuclein, excepting uric acid, were observed in the urine of a patient fed on nucleins. The excretion of uric acid seems to be dependent on the kind of food eaten. When guanin was added to the nuclein, the uric-acid excretion was noticeable.

Klemperer says that increase of uric acid is a secondary matter.

Edsall does not believe that uric acid causes any notable evidences of intoxication, nor that it produces the decided general symptoms of the disease. Uric acid, however, may produce much of the local trouble both in the attack and in the interval, by means of its local toxic action when present in extremely concentrated form. He believes the main cause of the intoxication to be due to some substance as yet unknown. There is no more reason for believing the xanthin bases to be the cause of gout or of the uric-acid diathesis than many of the other toxic excretory substances.

His and Hagen do not believe that as yet any reliable method has been discovered for estimating the purin bases.

Ross states that the cause of the gouty paroxysm is still unexplained. Duckworth considers gout a neurohumoral disease, dependent on faulty metabolism and on a neurotrophic disorder. There is then probably an excess of uric acid formed and a periodic retention of it in the blood. He attributes the paroxysm to nervous influences which are under the control of a bulbar centre. This neurosis is related to the arthritic diathesis. During a crisis the solubility of the urates in the blood is changed, as a result of which biurate of sodium crystals are formed and deposited in different parts of the body. Uratic deposits may occur accompanied by no pain or paroxysm.

Gore ascribes the existence of gout not to the presence of uric acid in the blood but to a toxin which is formed by the action of certain bacilli on an altered secretion of the intestine. The effect of the toxin on the liver is the production of uric acid. Diet alters the intestinal secretions, and heredity is an added factor in the etiology of this disease.

As to the influence of heredity, Osler states that statistics show that this disease existed in the parents or grandparents of from fifty to sixty per cent. of the cases studied. Although gout rarely develops before the thirtieth year, it has been seen in nursing infants. In a large number of cases its first symptoms are noticed before fifty years of age.

Bain says the alloxur bodies in gout are not increased.

Burney Yeo discusses irregular gout and believes it due to "hepatic inadequacy." The liver is a factor in the formation of urea and uric acid and in the metabolism of the nitrogens and carbohydrates.

Freudweiler by his experiments has shown that a lesion which has an anatomical correspondence with that of true gout can be caused by the injection of sodium biurate into the tissues. The biurate seems to exert a poisonous effect. The lesion thus caused is disposed of by means of phagocytosis.

According to Stengel and Edsall, there is considerable proof that

gout is not due to an excess of uric acid in the blood—that uric acid is not the materies peccans of this malady. Edsall calls attention to an important fact which has recently been determined—that, generally speaking, the larger part of both uric acid and the xanthin bases comes from the food. Stengel believes that whatever may be the active agent in causing gout, diet is a most important consideration in its etiology.

Symptoms.—There is little new in this direction. But there seems to be a tendency to ascribe many obscure conditions to the gouty diathesis, especially those concerning the digestive organs, the mucous membranes, the nervous system, and the organs of special sense, particularly the eye. A very obscure condition is gout of the stomach. According to Grube, gout of the stomach sometimes takes the form of nervous dyspepsia. In other cases there are varied symptoms of the digestive tract. The patient may suffer extreme pain; there may be mucous vomiting, decrease in the secretion of hydrochloric acid in the stomach, with resulting fermentation. The tongue is often fissured and sore, and looks like raw beef. The bowels are constipated as a rule, with putrefactive fermentation. Even in cases of this kind the appetite is sometimes excellent. Lithæmia of childhood is so called, often with little proof. There is a case of asthma on record in which the symptoms were greatly ameliorated by the administration of colchicum.

The symptoms of irregular gout, as described by Burney Yeo, are frequently pale fæces due to the absence of bile pigments. They are often extremely offensive. Sometimes there is constipation and in other cases diarrhœa. The appetite is often poor, while the patient complains of a sweetish-bitter taste in the mouth. The urine has a high specific gravity and is highly colored, and as a rule is very acid. The liver is somewhat enlarged and is tender on pressure. The attacks of irregular gout are more frequent during the cold northeast winds of spring. The skin becomes chilled and more work is thrown on the internal excretory organs.

Diagnosis.—Edsall declares that from a diagnostic standpoint, estimation of the amount of uric acid in the urine, whatever the method used, is absolutely without value. The condition called uric-acid diathesis cannot be estimated in this way.

Luff gives as differential points in the diagnosis of rheumatoid arthritis from gout, the gradual onset without much swelling and the marked symmetry of the former disease and the frequent involvement of the temporomaxillary joint which is never affected in gout. He believes this disease to be infectious and does not admit the theory of its nervous origin. He thinks that gout may coexist with arthritis deformans, and that rheumatism may predispose to it.

Stengel points out an important point in diagnosis—that arthritis showing the clinical characteristics of articular rheumatism, when not occurring for the first time till after the fortieth year, is very apt to be gouty in character.

A fatal case of gout is reported by Strumme in which at the last the symptoms were those of nephritis, swelling of the lymphatic glands, and cachexia. Autopsy disclosed extensive amyloid degeneration.

Treatment.—Stengel declares that the only way to treat gout with success is to direct the *diet.* Restricted diet gives excellent results. Burney Yeo believes that the simplest diet is the best. Pounded lean meat, with hot water as a drink, is the easiest for the feeble digestive organs to assimilate.

Adams advises abundance of water. The drinking of milk is to be encouraged. He limits the amount of salt on account of its tendency to form sodium biurate. He advises fats and sugar, and the different starchy fruits and vegetables.

Gee advocates a large cup of fresh whey to be taken after every meal to prevent uric-acid gravel from forming in the urine. Much is said about the necessity of exercise and this is without question most valuable. But gouty subjects are often very energetic and demand rest, especially after middle life, when the excretory organs are not adequate to dispose of all the waste products in the body.

Martyn speaks of the treatment of gouty eczema. He divides this affection into acute and chronic. Of the former there are two varieties, dry and moist, and he speaks of a latent form of chronic eczema. The symptoms are a burning and itching of the skin with no visible lesion. For this trouble a lotion or ointment with carbolic acid is soothing. Rigid diet is indicated with no alcohol; and alkalines should be freely given. He advises the gouty patient to avoid the fruits containing much fermentable sugar or acid, especially rhubarb, strawberries, gooseberries, lemons, apples, and also stimulating food.

Ransom contributes some interesting views concerning diet. He prescribes meat freely. He thinks animal food is best in these cases. He withholds carbohydrates only when obesity is a prominent symptom, or when they are contraindicated for some special reason. Fats do not seem to have any particular effect and may well be used, especially in those cases in which the carbohydrates are curtailed. He approves of a mixed general diet with a fair proportion of vegetable food. As to alcohol, he quotes the experiment of His in which he injected acid sodium urate into subcutaneous tissue. The capsule which forms around the nodule is transformed into young connective tissue. If then alcohol be given to the animal in repeated small doses, the capsule becomes fully formed connective tissue from which the

acid is less able to be eliminated. In the aged or feeble, however, whiskey may be given in small quantities with good effect.

Clothing is very important. The healthy action of the skin must be preserved. Wool is the best material theoretically, but is often irritating. In such cases cotton woven in cellular form is best. The skin is ventilated and sudden chilling is avoided. There should be as little change as possible during the various seasons.

Climate has a marked influence. The seashore is the worst for this disease. Cold, dry weather is often beneficial. An equable and fairly bracing climate is best. Various places in this country regarded as health resorts for gouty patients are Hot Springs, Va.; Las Vegas Hot Springs New Mexico; Poland, Me.; Richfield, N. Y.; Klamath Hot Springs, Cal.; and the "Vichy Spring," Saratoga. The Egyptian climate is said to agree with gouty patients.

Baths are often most valuable in aiding elimination of waste products. There are various kinds. Mud baths are often followed by happy results. A calcium-sulphate bath is good for dry, irritating, scaly eczema. It should never be over 98° F. The body should be dried and powdered afterward.

Medicinal Treatment.—The individual should be treated rather than the disease. Ross advocates a pill of colchicum and mercury given at night and a saline aperient in the morning. This will improve the general condition and ward off gouty attacks. Colchicum is the best remedy in acute gout. It is sometimes of use in chronic gout. Piperidine is said to be the best solvent of urates.

Bain states that potassium iodide seems to delay the development of renal and cardiovascular changes. It is contraindicated in advanced kidney disease. Guaiacum is probably the best eliminator of uric acid. The alkaline treatment is practically restricted to disorders of the alimentary tract. He adds that sodium salicylate and thymus increase the excretion of uric acid in gout.

Burney Yeo is an advocate of the use of sodium salts and other alkalies in the treatment of irregular gout since they act on the stomach, intestines, liver, and kidneys, and favor metabolism generally. There is no better expectorant than a warm solution of sodium bicarbonate, in the "dry" or "gouty" catarrh of the air passages.

Sternfeld likes quinic acid in gout. In the body it is changed to benzoic acid and this into hippuric, which is far more soluble in water than uric acid. Quinate of lithium combined with a diuretic is advised. Tablets of seven and a half grains each are given. Ten of these may be given daily.

Hermann finds glycerin valuable as a solvent of uric-acid calculi. He gives from one to four ounces in an equal amount of water between meals for a few days. He considers it a lubricant.

Salfeld advocates sidonal (a compound of quinic acid and piperazin) in both acute and chronic gout. He uses the powdered drug five or six times a day in fifteen-grain doses.

Nicolaier advocates urotropin as a solvent of uric acid.

Galvanism is recommended by Guilloz. By it the diseased tissues are better nourished and substances which dissolve the urates are brought to the affected joints by means of cataphoresis.

Massage is often helpful in the treatment of affected joints.

The spa treatment is valuable when all of its details are carefully looked after. The patient is then constantly under the eye of the physician.

The hot-air treatment has recently received much attention and has met with success, in both acute and chronic gout. Various devices have been invented for its application. The affected part can be subjected to a temperature of from 250° to 300° F., or higher, for an indefinite time while the air surrounding the part is kept dry by allowing the evaporated moisture to escape at intervals. In acute gout the inflammation and pain are quickly reduced and in chronic cases the increased circulation effectually eliminates by skin and kidneys the morbid products in the blood.

ARTHRITIS DEFORMANS.

BY

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THE seven years which have elapsed since the publication of the article on arthritis deformans in the second volume of this work have brought about conspicuous changes in the prevalent views as to the nature of the morbid conditions which are commonly included under that name, nor can it be claimed that any finality has yet been reached.

Many of the ideas which formerly held the field have been seriously shaken, and it is recognized that the whole subject calls for reconsideration in the light of the advances of modern pathology. On the other hand, the newer notions have not yet assumed such definite forms that one can discuss them in any but a tentative manner. Such a period of transition is clearly not a favorable one for reviewing the present position of the subject, and one cannot do more than attempt to reflect the drift of opinion among those whose minds are directed to its investigation.

In the earlier article some stress was laid upon the wide clinical differences which exist between the various conditions usually spoken of by such names as arthritis deformans, rheumatoid arthritis, or osteoarthritis, and nowadays there are not a few who believe that these differences indicate more than mere variations of a single disease. In a word, that what has been called arthritis deformans is not a definite morbid entity, comparable to gout or to acute rheumatism, but rather a congeries of joint affections, more or less chronic in their course, and which call for further differentiation and classification.

This much may be regarded as certain, that the classical description of the changes in the joints in osteoarthritis, the fibrillation and erosion of cartilages, the formation of osteophytic outgrowths, and the grooving and eburnation of the articular surfaces of the bones, does not by any means hold good for all the cases included in the clinical category of arthritis deformans, whereas they are met with in some other conditions not usually so classed, as in the arthritis of hæmophilia. It is in the chronic articular lesions of elderly people, which are so

often confined to a single joint, that such changes are seen in the greatest perfection, and indeed it was from such cases that the description was originally drawn.

Among the conditions included under the name of arthritis deformans there is one at least which has such distinctive characters that it may justly be regarded as a distinct disease. This is the multiple arthritis usually met with in younger women, but which may attack either sex, and which is accompanied by well-marked fusiform swellings around the affected joints. This is essentially a disease which runs its course, although that course may be a long one, and may be lengthened out by repeated relapses, and although it may leave behind it life-long deformity and crippling.

In the acute or subacute stages there is usually definite febrile disturbance, with an evening rise to 100° or even 102°, and an increased pulse rate which is out of proportion to the pyrexia, and which may persist for a long time after the temperature has returned to within normal limits.

Although the articular structures are so seriously affected, and the disease often spreads so widely that hardly a joint in the body escapes, there is very little tendency to visceral complications, and in watching such a case one does not anticipate the development of cardiac lesions.

The distribution of the arthritides is somewhat characteristic, and the joints of the vertebral column and the temporomaxillary articulations, which are little liable to be affected in acute rheumatism, are very often involved. The hands are practically always affected and in many cases are the first parts to suffer. The fusiform swelling of the first row of interphalangeal joints and of the wrists, coupled with the wasting of the interosseous muscles, gives to the hands a very characteristic appearance. The swelling appears to be chiefly of the soft parts around the joint, and is increased by the effusion of fluid into its cavity. In this as in other long-lasting joint diseases the wasting of muscles is a very conspicuous feature, and as the disease subsides the wasted muscles tend to undergo contracture, and to this are due the somewhat grotesque deformities and greater or less immobility which unfortunately result in so many cases.

If the distinction here drawn between the active stage and that of resulting deformity is a sound one, its recognition is clearly important from the points of view of both prognosis and treatment.

The malady has so little fatal tendency that opportunities are seldom afforded of examining the affected joints during the active stage. Dr. Bannatyne, speaking of the appearances at this stage, describes swelling and matting of the synovial membrane and ligaments, commencing ulceration of the articular cartilages at their margins,

and occasionally on the articular surfaces, and the absence of any outgrowths or lipping.

In a case recently under the care of Dr. Hale White in Guy's Hospital, death occurred during the active stage from intercurrent typhoid fever, and he has kindly allowed me to read in advance a paper on this subject which will appear in the fifty-seventh volume of the Guy's Hospital Reports, and to quote from it the following points: The swelling was found to be chiefly due to chronic inflammatory changes in the tissues around the joints, and to a lesser extent in the synovial membranes. The only lesions of the cartilages observed, with the exception of a small erosion on the condyle of one femur, was slight erosion of the peripheral portions, only recognized on microscopical examination, and apparently produced by the pressure of swollen synovial fringes. In none of the many joints examined were there chondrophytic outgrowths and no osteophytes were anywhere found. He sums up his observations by saying that the lesions found were suggestive of a very chronic inflammatory process, commencing in the mucous membrane, and involving the tissues around the joints, and that there were no traces of primary changes in the cartilages or bones.

There is much to suggest that this disease has a bacterial origin, and bacteriological examinations of such cases have been carried out by several observers. The most extensive researches of this kind were those of Bannatyne, Wohlmann, and Blaxall, who in all but one of a series of twenty-five cases isolated a short bacillus of dumbbell shape, and with well-marked polar staining, which gave to it the appearance of a diplococcus. It could be stained with fuchsin or methylene blue, but not by Gram's method. It was cultivated on broth and on agar-agar. The organism was found in the synovial fluid and in a few cases in the blood also. It was not found in cases of synovitis of other kinds. Chauffard and Ramond, who describe enlargement of the lymphatic glands in the neighborhood of the affected joints as a feature of the disease, obtained from scrapings of the enlarged glands and from the synovial fluid a short, slender diplobacillus, which in many respects resembled that described by the English observers, but which was not decolorized by Gram's method. They were unable to obtain cultures of the organism.

Von Dungern and Schneider examined a case in which the more chronic joint trouble was preceded by an attack of acute rheumatism, and in which an erosion of the cartilages, especially in their peripheral portions, was observed, but no chondrophytes were present. In the articular fluid they found a very small diplococcus which stained by Gram's method. The organism was cultivated, and when injected into the knee-joints of rabbits produced changes similar to those observed

in the joints from which they were obtained. The same organism was also isolated from the liver and from the contents of the gall-bladder which showed signs of chronic inflammatory lesions. Von Dungern and Schneider regarded the gall-bladder as the source of the infection which produced the articular lesions. In Hale White's case also a diplococcus was isolated which failed, however, to reproduce the disease in animals.

The bacillus described by Max Schüller was isolated from joints in which there were abundant synovial tufts and fringes, and were probably the seats of a different morbid process. The bacilli when injected into the joints of animals reproduced a similar condition.

A disease which is somewhat similar in its clinical and pathological features to the acute or subacute arthritis deformans of adults is met with in children. In them a fatal ending is much more frequent, and opportunities more often occur for the post-mortem examination of the diseased joints. The characters of this disease have recently been described and discussed by G. F. Still in a paper which forms a valuable addition to our knowledge of the subject. In some of the cases which he examined the peripheral pitting of the cartilages was much more conspicuous than in Hale White's adult case, and was very obvious to the naked eye. In many instances there was marked enlargement of the lymphatic glands and of the spleen, and there were usually pericardial adhesions. The course of this disease is quite unlike that of true rheumatism as seen in children, but whether or no it is identical with the acute arthritis deformans of adults must be looked upon as still an open question.

The question whether the acute arthritis deformans of adults bears any direct relation to acute rheumatism is of much interest, but one to which it is not easy to give a definite answer. In the great majority of cases there is nothing in its onset or course suggestive of a rheumatic origin; but it cannot be denied that cases are sometimes met with in which a condition apparently identical appears to develop as a sequel of acute rheumatism accompanied by cardiac lesions, or is preceded by minor articular troubles, of a transitory nature which yield to salicylic treatment.

It is to such antecedent attacks of rheumatism that lesions of the cardiac valves, when present, may usually be clearly traced. The occasional appearance of subcutaneous nodules has been adduced as lending further support to the rheumatic theory, but in the rare cases in which such nodules are met with the patients have usually passed the age at which subcutaneous nodules are apt to develop in the course of true rheumatism, and the nodules themselves are much more persistent.

It may be that, as Dr. Cave of Bath has suggested, the disease

which we are considering does not result from infection by a definite specific organism, but that in different cases different organisms may be concerned, among which that which produces acute rheumatism may have a place. However this may be, it is only in a small minority of instances that the suspicion of a truly rheumatic origin arises.

The usual predisposing causes of the malady are such as tend to produce debility, such as rapid child-bearing or menorrhagia. Of recent years the onset has frequently followed attacks of influenza. In some instances a local septic condition, in the mouth or elsewhere, appears to play the chief part in its causation, and it is important, in any given case, to exclude the presence of any such condition, or if possible to remove it.

The disease is not confined to younger individuals, although most commonly met with at a comparatively early age; and sometimes it assumes a very chronic form, slowly spreading from joint to joint without passing through any definite acute stage.

Among the conditions included under the name of arthritis deformans is another disease which implicates many joints, which also is more common in women than in men, and is most apt to commence at or about the period of the menopause. In it the enlargement of the joints is firm and nodular, and is due to lipping of the cartilages and bones and the formation of osteophytes. In the distribution of the lesions and in the tendency to symmetrical invasion of the small joints the two diseases show a certain superficial resemblance, but in the details of distribution they differ considerably. Thus in the malady now under consideration it is the end joints of the fingers that are usually first attacked, and the carpometacarpal joints of the thumbs suffer with a peculiar frequency. Just as the former disease may occur at an unusually late period of life, so the latter is occasionally met with at an unusually early age, but still shows its characteristic features from the outset. The lesions present in such cases correspond with those found in the monarticular forms, such as the hip-joint affection of elderly men, but on clinical grounds we are justified in regarding these latter as constituting yet another distinct group of cases.

This nodular form of the disease is that in which there is most ground for suspecting a dystrophic origin; but the dystrophic theory is nowadays regarded with much less favor than formerly, and it must be mentioned that from the knee-joint of a man of sixty-seven years in which osteoarthritic changes were present Poynton and Paine recently succeeded in isolating a diplococcus which, when injected in the circulation of a rabbit, produced a disease of one knee-joint, accompanied by similar osteoarthritic changes, including erosion of the cartilages and heaping up at their edges. This observation, if borne

out by further researches on similar cases, will afford evidence that even here also we have to do with a form of infective arthritis.

It is not improbable that the process of subdivision may be carried still further as time goes on, and that we shall come to recognize other joint lesions, distinct in their nature, among those which have hitherto been classed with the above under the general name of arthritis deformans. Even a third affection of many joints may eventually be differentiated, much less common than those which have been referred to, in which fixation and deformity are extreme, even from the early stages, whereas there is very little swelling of the joints. In such cases peculiarly sharp osteophytes are apt to be developed, and true bony ankylosis may occur in the diseased articulations.

Treatment.

The general rules as to treatment mentioned in the earlier article, and which are based upon the accumulated experience of many practitioners, independently of any theory as to the nature of the disease, still hold good, but it is clearly important that we should take into consideration the nature of the particular case, and as regards the more acute malady whether we are dealing with its active stage, or with the deformities and other effects which it leaves behind it.

The recognition of the fact that a local infective process may be its starting-point makes it necessary to look out for such causes and to treat them when present. Of no less importance is the treatment of such troubles as menorrhagia or metrorrhagia when present, which tend to weaken the patient and so favor the progress of the malady.

The part played by muscular contracture in the production of the ultimate deformities renders it desirable to counteract the muscular atrophy as far as possible, and much may be done in this way by skilful massage of the muscles when the active stage is passing off.

As long as the trouble in the joints is active the massage should be limited to the muscles, but at a later stage manipulation and movements of the joints may be of service to restore their mobility.

The same applies to the various forms of hot-air and radiant-heat baths which have been extensively employed of late years. When the disease is no longer active they not infrequently prove of much service in removing stiffness and in relieving pain.

No drug has yet been found to exert any specific curative action in these cases, but in addition to tonic medicines Bannatyne has obtained very good results with certain remedies such as guaiacol carbonate, salophen, and salol, and in a certain proportion of cases in which intestinal antiseptics are indicated he has found β-naphthol very useful.

As outward applications he recommends guaiacol in olive oil and salicylate of methyl, which may be painted upon the joints and covered with lint and oil silk. The objection to both these remedies is their somewhat overpowering odor.

In the nodular form treatment has much less effect, but here also tonic treatment and a generous dietary prove of service, and some benefit is derived from massage and electrical treatment.

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DISEASES OF THE SKIN.

BY

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NEW YORK.

DURING the few years which have intervened since the volume on skin diseases of THE TWENTIETH CENTURY PRACTICE appeared, there have been advances made in various departments of this special branch. In the limited space available these can receive but brief mention, and, in order to give space to those changes of views and methods of treatment which seem to indicate real progress, much which may be of value but which is still in doubt will have to be omitted.

Microorganisms as etiological factors in skin affections have attracted a large share of laboratory attention, and culture methods, with the improved technique of recent times, open up fields of research previously little explored. There no longer exists a reasonable doubt that bacilli and cocci play a most important rôle in the onset as well as in the perpetuation and modification of a long list of diseases, and the importance of this line of investigation is constantly growing.

Besides the pathogenic organisms constantly present in tuberculosis of the skin, leprosy, anthrax, rhinoscleroma, and other affections, we have the Staphylococcus pyogenes aureus as the most commonly distributed and readily discovered in all forms of pustular affections, abscesses, sycosis, furuncle, panaris, and carbuncle. Staphylococcia has come to be a not uncommon designation for pustular affections or pyodermias, in which these organisms are found, and still it is admitted that they may not be the sole cause of suppurative processes.

Gilchrist, of the Johns Hopkins University, has found that the Streptococcus pyogenes is more prevalent in some series of investigations than the Staphylococcus pyogenes aureus and albus, and the important point has been brought out by him that among other pus producers are to be numbered the Tinea megalosporon ectothrix and endothrix, the tubercle bacillus, blastomyces, and protozoa.

The Streptococcus pyogenes is the organism encountered in pyæmic diseases. While Fehleisen's special streptococcus has been accepted as the cause of erysipelas, Pfahler[1] has found in eight cases a diplo-

coccus which he believes to be the cause of erysipelas or of a disease which we cannot at present distinguish clinically from erysipelas. This diplococcus he has cultivated, inoculated into rabbits, and obtained again from the diseased tissues of these rabbits, thus conforming to Koch's postulate.

Following the order of arrangement in Volume V. we may first consider a few advances made in

Animal Parasitic Diseases.

Myiasis, or the condition resulting from the presence of various fly parasites in the skin, has received attention at the hands of Dr. James J. Walsh.[2] The screw-worm fly (*Compsomyia macellaria*) may deposit its ova in putrid ulcers where the larvæ or "screw worms" may produce severe irritation and injury. The larvæ are less than half an inch long, of bluish-green color, with metallic reflection, distinguished from related forms by three longitudinal black stripes on the thorax. The head is reddish or yellowish; its body is covered with stiff black hairs. Three or four hundred eggs may be deposited by a single female within the space of a few moments. Under the microscope the eggs show a prominent ridge. They may hatch within nine hours. The maggot may burrow into the tissues and matures within a week. The fly occasionally deposits its ova in the nostril of a sleeping individual, causing redness, swelling, and pain in the nose.

I have observed in this city a deep ulcer of the leg extending along the side of the tibia literally filled with maggots, whose presence accounted for the great depth of tissue destroyed. The wound healed promptly after their removal and the free use of carbolic-acid solution. This drug is recommended in from three- to five-per-cent. solution, to which the United States entomological expert thinks glycerin may be advantageously added.

The caterpillar may excite persistent and annoying pruritus with urticarial lesions, becoming at times confluent. Jams C. White[3] relates several instances observed by him in which the larva of the *Euproctis chrysorrha*, or brown-tailed moth, was the supposed cause. Erythematous lesions appeared chiefly upon the neck shortly after known exposure to the caterpillar.

The most recently recommended application in *scabies* is peruol, which Sachs[4] has used successfully in thirty-five cases; and sulphur lotum, which Sherwell[5] has employed in a large number of patients. Peruol is a thin, colorless, and almost odorless oil which is supposed to contain the active elements of balsam of Peru. It does not irritate the skin as a rule, and is best used diluted with three parts of castor oil to be well rubbed into the skin three or four times.

In applying the sulphur powder no great amount of friction is required, and half a drachm suffices for each application; but a like amount should be sprinkled upon the bed-covering which comes next to the patient's skin, as well as upon the inner surfaces of the underclothing. It is much more cleanly than the sulphur or other ointment and is usually very effective. I have used this method myself now for several years with gratifying results.

The statement is usually made that while the *Demodex folliculorum* is commonly present in dilated sebaceous follicles and comedones it produces no disease of the skin and causes no inconvenience. The writer has long thought that this prevalent opinion might be erroneous, and several years ago he presented before the New York Dermatological Society a woman with a small papular eruption upon the face which resembled the early stages of disseminated molluscum contagiosum. It was somewhat itchy and irritating. Examination showed a large number of the Demodex folliculorum present in these little papules and surrounding follicles. The opinion was then ventured that this acarus was probably not so innocent as had been supposed. A cure was effected under applications of ammoniated mercury ointment before an opportunity to examine the case further was presented. Dubreuilh[6] has reported an instance of long persisting pigmentation of the face in a woman whose hair follicles were prominent and from which a minute horny spine projected, causing a roughness of the surface. This condition persisted after three months of vigorous treatment, the Demodex parasites being still present. Three instances of similar nature reported from Italy are referred to.

Water itch, which is the name given to a superficial vesicular dermatitis attended with severe pruritus, attacking the feet of coolies, especially those who work barefooted in tea gardens, is believed by Dr. A. B. Dalgetty[7] to be due to an acarus resembling that of scabies. The irritation begins in the clefts between the toes and spreads over the dorsum, but rarely beyond the ankle. The vesicles may coalesce, become bullous or pustular, and while a crust rarely forms, a large slough may result in a troublesome ulcer.

The disease affects those who work in the older tea plantations whose soil is moist and fertilized with fecal matter. It disappears in the dry season. The acarus which he has found and described has an ellipsoidal body, slightly narrower toward the head, and a glass-gray color. The male is 0.18 mm. long and 0.08 mm. broad; the female being 2 mm. longer and 1 mm. broader. No organs of vision and no respiratory apparatus were detected. The larva is smaller and has three instead of four pairs of legs. The anatomy would seem to place the mite among the *Rhizoglyphinæ*, and the writer suggests the name ***Rhizoglyphus parasiticus***, and believes that this

species has hitherto been unknown as a human parasite, and that it becomes so only under certain favorable conditions. The treatment suggested is the application of a strong solution of lime and sulphur. Recurrences are frequent, and as a prophylactic measure he urges the wearing of tightly fitting high shoes.

Megrim [8] describes an acute inflammatory œdema of the hands and arms, caused by the ingestion of young spiders, which adhere to the shoots of l'Aroche (*atriplex*).

The question of transmission of *animal scabies* to man has received attention from Alexander,[9] who reports several such cases. He holds that when an itch depending upon sarcoptes exists in animals coming into contact with human beings it may be transmitted. Regions usually affected in scabies are exempt as a rule in this form, while the itch mite is difficult of detection and burrows are not common.

Vegetable Parasitic Diseases.

Ringworm has continued to attract considerable attention, since Sabouraud's brilliant work resulted in the separation of the disease into a variety of forms depending upon distinct fungi. While most accept the proposition that the microsporon is a distinct species and produces a clinical picture differing from that caused by the megalosporon, others do not admit a multiplicity of fungi, but invoke other causes to account for the varying size and form of the microscopic growth and the diversity of effects produced upon the skin. Given [10] finds the Microsporon Audouini present in all clinical cases presenting a characteristic dusty white or frost-like sheath extending up around the broken stumps of hairs. It may be present also when this circumpilar collarette is absent. Contrary to Sabouraud's observation, he finds the microsporon not more difficult to cure than other forms. Bunch [11] thinks greater reliance must be placed upon cultures than upon the microscope alone in diagnosis. When the spores are closely packed together, their shape is distorted and difficulty is encountered in distinguishing between the Microsporon and the Megalosporon ectothrix. He reports eight instances of transmission from animals.

Sabrazes and Breugues [12] mention a peculiar form of ringworm resembling a small carbuncle, which was excised and found to contain mycelium and spores. In ringworm of the nail, which may persist for many years, usually unrecognized, the fungus is not readily detected. Crocker [13] points out the necessity of soaking the scrapings from the nail for a long time in liquor potassæ. Johnston [14] advises applications twice daily of a saturated solution of pure iodine in a saturated solution of iodide of potassium.

Gottheil [15] holds that effective treatment of scalp ringworm must include measures to open up the deeper collections of parasites in the

hair follicles and shafts of those hairs whose papillæ are seated deeply in the corium, or even in the subcutaneous connective tissue. Persistence in the repetition of courses prescribed will alone bring permanent results. All pustules must be opened and crusts and scales removed. The hair around the patch must be kept short. The dermal curette must be used, but not vigorously. The patch and surrounding margins to the extent of from a quarter to a half-inch should be epilated with forceps. After washing with green soap chrysarobin in five- to ten-per-cent. ointment should be applied. The forehead may be protected with strips of plaster. After sufficient inflammatory reaction sulphur and ichthyol ointment can be substituted for a few days. Jamieson [16] uses a superfatted potash soap for washing. His favorite prescription is:

℞ Precipitated sulphur,	ʒi.
Salicylic acid,	
Beta-naphthol,	
Ammoniated mercury,	ää gr. x.
Lanolin or vasogen,	ʒi.

As a prophylactic measure for unaffected areas Sabouraud [17] advises tincture of iodine diluted with three or four volumes of alcohol (ninety per cent.), to be applied three nights of each week. On the alternate nights an application is made of pyrogallic acid 1 gm., oil of cade 4 gm., benzoinated lard 20 gm.

Tinea Versicolor.—Several points have been brought out during the past few years in regard to chromophytosis. Despite the locations commonly invaded and the ease of detecting the fungus, mistakes in diagnosis are not uncommon, especially in atypical forms. I have directed attention [18] to the disease as it affects the face and pubic regions, while Powell [19] tells us that in Assam face implication is not uncommon. Gottheil [20] describes and depicts lesions simulating leucoderma limited to the cheek of a negro, while both he and Abrahams have shown instances in which the palms were implicated.

In the pubic region patches of chromophytosis are apt to escape detection and treatment and thus serve as a focus for renewed outbreaks after apparent cure. Deep-seated follicular invasion is likewise misleading, and it is here also that the iodine test to which I have referred [21] as an aid to diagnosis and to the description of which Sobel [22] has devoted a chapter, finds a sphere of usefulness both in detecting hidden fungus and as an excellent mode of treatment. The same author has recently further considered the relation of dermatomycoses to this test,[23] which he also finds of value in differential diagnosis and classroom demonstration. As to treatment, Gottheil employs a one-per-cent. formalin solution as a general wash, or a strong solution of sodium hyposulphite. In common with others I have found iodine

applications of decided value. Porasz[23] advises several applications daily of the tincture until decided desquamation ensues. Gottheil uses bichloride of mercury in tincture of green soap (1:3,000). It is well to use in bathing a sand-soap or pumice-stone soap. Levy[24] applies for three days pure lysol once a day; afterward one-half- to one-per-cent. solution as a wash. Radiotherapy has been advocated in mycoses of the skin in general, but no specific reports upon the effects in chromophytosis have appeared.

Favus.—The older belief that favus confines its ravages to hairy parts is refuted by a case recently reported by Glück in which lesions occurred upon the prepuce and glans penis.

While there are undoubtedly almost as many morphological varieties of the Achorion Schönleinii as there are different forms of the ringworm fungus, the view has of late been gaining supporters that in the human subject at least there is but one offending or etiological organism which is capable under varying conditions not only of producing different clinical forms, but of appearing differently under the microscope. Schliessner[25] has added to the list of youthful subjects of favus an infant of nine days with lesions on the cheek contracted from the mother, and another fifteen days old with lesions upon the forehead contracted from another child having the disease. Favus limited to the nails is not so common that I should refrain from the mention of two instances in young women presented by me at the New York Dermatological Society.[26] They were both treated by radiotherapy, but ceased attending before it could be said that a cure had been effected. The yellowish-white points mentioned by Kaposi could be made out in one case in the bed beneath the external nail plate.

In the matter of treatment of scalp favus no method which does not include epilation can be depended upon. Even the *x*-ray, unless it of itself causes falling of the hair, should be supplemented with extraction in the older way. Jadassohn[27] advises a five- to ten-per-cent. pyrogallol ointment associated or not with *x*-ray treatment. Personally I have observed decided effect from radiotherapy, but prefer to employ other measures at the same time. That the usual parasiticides have little effect upon the fungus itself would appear from the experiments of Calderone[28] with cultures.

Formalin solutions have been widely employed. Demidow[29] removes the crusts with a five- to ten-per-cent. solution, applies it to the affected scalp, and bandages the head.

I have used formaldehyde solutions rather extensively, but have found the stronger applications extremely painful, though for the most part efficacious. A one-per-cent. solution is strong enough as a prophylactic wash for the unaffected portions. The strong solutions should so far as possible be applied by the physician to limited areas

of the disease. In the nail cases, aside from the *x*-rays, I have had the best results from strong iodine solutions.

Pinta Disease.—It has been found that the active parasite in this contagious affection, known also as carates, belongs to the Aspergillus family, and is found chiefly in the outer layers of the epidermis. There are present fine filaments with hyphæ terminating in clubs surrounding chaplets of spores, and sterigmata encircle the sporulating elements. Discovery of the fungus serves to distinguish the "spotted sickness" from the chloasmas, macular lepra, tinea versicolor, pityriasis rubra pilaris, etc., which it might resemble.

Actinomycosis.—Some advances are to be noted in the therapy of "lumpy jaw." Iodide of potassium has so far taken the place of extensive surgical procedure that it might be called the medical scalpel. While it does not cure all instances, it should be preferred to extensive cutting.

Gautier has advocated an electrochemical method. He inserts into the growth under anæsthesia two platinum needles, connected with the opposite poles of a battery, and passes a current of fifty milliampères. A few drops of a ten-per-cent. solution of iodide of potassium are injected simultaneously. Silberschmidt's[20] studies lead him to state that a variety of growths are capable of producing the clinical picture and that at present a differentiation between actinomycosis and pseudo-actinomycosis is not possible. Lubarsch[21] says the ray fungus must be classed as a subdivision of streptothrices.

Erythema.

E. induratum.—There is little of novelty amongst erythematous affections, but that produced by Finsen's ray is very similar to ordinary sunburn, and is often accompanied by similar pigmentation. That produced by the *x*-ray is assuming greater importance from the greater use of the ray in therapy. It is usually of ephemeral duration and unless the exposure is repeated has no serious significance.

E. iris has been described in a series of cases following vaccination by Walker.[22] Gilchrist, White, Corlett, and Sobel have described similar conditions. Those described by the latter were in cases from my own clinic.[23] An erythematous eruption resembling measles usually occurs in about ten days after vaccination, and eruptions resembling Erythema multiforme were observed a number of times.

E. induratum has been examined histologically by McLeod and Ormsby,[24] who found marked infiltration around the thickened blood-vessels, of which all the coats were involved. Giant cells were present more or less completely surrounded by a ring of nuclei. There was close resemblance to a tuberculous nodule, but no bacilli were

found and inoculations were negative. In another case nodules showed typical tuberculous structure; no bacilli were found. The affection is always to be differentiated from E. nodosum, as it may occupy the same situations. From syphilitic gummata it is to be distinguished by an evolution continuing perhaps many years. Inoculation experiments have succeeded in the hands of Thiebièrge and Ravant.[35] Colcott Fox has also had a successful inoculation.[36]

Scarlatiniform erythemas are described as occurring in the prodromal stage of measles,[37] and also as occurring in the convalescent period of the same disease. Breton[38] describes this form of erythema following the hypodermic injection of cacodylate of sodium. Pascal[39] found that a scarlatiniform erythema was produced in a number of persons employed in sifting barley. The offending agent appeared to be an irritant dust produced by innumerable small butterflies which infested the grain. The rash was attended by severe itching and burning upon the exposed portions of the body.

In *E. nodosum* Brownlie[40] advises painting the lesions with ichthyol, ʒ ij.; spts. vini rect., æth., āā ʒ iij. Mix the alcohol and the ether together and add the ichthyol. This is said to give almost immediate relief from pain. Salophen will afford speedy relief if given internally. Jadassohn[41] reaches the conclusion that both E. multiforme and E. nodosum are infectious diseases to be classed with purpura and articular rheumatism. In forming this conclusion he has studied the literature which is partly covered by two hundred and twenty-seven recent articles. Gottheil[42] thinks we should recognize four varieties of polymorphous erythema: that of the ordinary type; E. nodosum; E. toxicum; and the E. metastaticum of septic processes, etc.

Eczema.

If we accept Morris'[43] definition, it opens the way to include much under this chapter. He says: "It is a disease, the most striking clinical character of which is the infinite variety of lesions by which it displays itself; originating in the action of parasites on the skin, the resistance of which has been enfeebled by pre-existing disease or structural abnormity, or by disordered innervation; sometimes made more intractable by gout and other constitutional states, but having no direct relation to the general health."

The view that general derangements act only in preparation of the soil is shared by many observers, including Lereddi.[44] That a microbic invasion is the essential cause is a theory that seems to be gaining supporters. Bulkley,[45] however, says the majority of dermatologists do not regard eczema as a parasitic disease, and look upon Unna's microorganism as a staphylococcus showing peculiarities of growth. His view regarding a predisposition in the seborrhœic state, and in

the circulation of toxins in the skin due to improper assimilation, etc., is shared by Duhring and Hartzell,[46] who say it is in accord with that of the majority of observers. Schultz and Roll[47] take the opposite view, having found the Staphylococcus pyogenes aureus almost constantly present in sixty cases examined. Most observers, however, look upon this organism as an evidence of secondary infection and answerable for many of the complications. Inoculation experiments are almost without results, and the primary lesions are usually found free from suspicious organisms.

Neisser says there is no such thing as eczema, the name being given to a group of diseases. He accepts E. seborrhoicum as a parasitic affection, but in other eczemas microorganisms exist only accidentally.

In treatment there seems to have been little advance. There is a general tendency to do away with ointments in eczema and to substitute lotions, or preparations having the nature of protective dressings—*pastes*, *varnishes*, etc. The tendency to apply strong irritating and stimulating drugs and to give arsenic internally is to be deprecated. A watery solution of methylene blue is often serviceable, but has the disadvantage of its color and staining qualities. In chronic eczema Gautier[48] has had some success with cacodylate of sodium. Walsh[49] employs vasogen, ʒ ij. to ʒ iv., in vaseline ʒ i. and has found it extremely valuable in eczemas of the palm. The *x*-ray is amongst the newest, and possibly the best, forms of treatment for certain inveterate eczemas. Hahn seems to have been the first to use this method in 1899, and it has since been quite extensively applied in all scientific centres. In intertriginous eczemas of childhood Leistikow[50] advocates pyrogallol in two-per-cent. strength, and from this down to one-half per cent. for the acute stages. The danger of absorption when extensive surfaces are covered by this drug must not be lost sight of. In very chronic processes, strong silver solutions effect a good purpose.

A new treatment advocated by Kromeyer and Gruenberg[51] is that of lanigallol, which is a triacetate of pyrogallic acid, but, unlike the latter, produces no ill effects on healthy tissue. In eczemas resembling psoriasis, the drug is said to split slowly into its component parts, and the freed pyrogallic acid exercises its counterirritant action upon these lesions. It is used in five-, ten-, or twenty-per-cent. strength made into a paste.

Dermatitis.

X-Ray Dermatitis.—The chief form dermatitis to engage our attention is that produced by the focus tube. The question is still unsettled as to whether the condition is due to the *x*-ray or to electricity. The majority of observers seem inclined to attribute the effect to the ray itself, and while individual predisposition undoubtedly plays an im-

portant part, the most essential factor seems to be the quality of tube from which the ray emanates and the proximity to the surface. The so-called low or soft tube appears much more prone to cause a radiodermatitis than the high or hard tube. The effects vary from an inflammatory erythema passing away rapidly with perhaps a slight desquamation, to the production of bullæ, followed by a repeated and pronounced exfoliation, excoriations requiring weeks or even months to heal over, and finally gangrenous dermatitis involving the deeper structures of the skin and even subcutaneous parts.

Delicate-skinned and youthful persons, and especially those of fair complexion, suffer more readily and more intensely than those whose skins contain an abundance of pigment.

A strong point to my mind against the theory of idiosyncrasy in favor of that of soft tube and intensity of ray is an experience of my own in which six patients developed a dermatitis after a low tube had been substituted for a high one, there having been no such effects in these or other patients during a long period in which the high tubes were employed. Against the theory that it is the *x*-ray alone that causes the dermatitis, Schiff and Freund have reported to the Wiener Aerzte-Verein that high-tension currents may produce dermatitis and alopecia. Twenty-minute exposures were made to the silent discharge of the negative pole of a powerful Ruhmkorff coil.

Much may be done in the way of prophylaxis both in radiography and in radiotherapy. Now that the latter is being so extensively applied in the cure of cutaneous and cancerous affections, Unna suggests the application of zinc jelly containing ten per cent. of cinnabar and oxychloride of bismuth. I have recommended and used extensively a three-per-cent. methylene blue paint. I have also devised protecting screens fenestrated for the rays to pass solely to the parts under treatment. A vulcanite plate with an opening, one to five inches in diameter, cut opposite the diseased area, has the advantage over similar metallic plates, that there is no disagreeable "sparking," and has appeared to furnish the requisite protection. Such a shield with tubular prolongations to offer additional protection when the rays are applied to the throat, uterus, rectum, etc., is now upon the market.

An additional effect is often noted—a pronounced pigmentation of the normal skin surrounding diseased areas. This may occur also without any noticeable dermatitis and indeed often seems to be a protection against the latter. According to Unna the effect is due to an increased pigmentation in the upper layers of the chorium. Whether the mode of action is trophic or chemical has not been determined. In the matter of treatment the same remedies may be employed as in dermatitis calorica.

Personally I have found methylene blue solution to act well in a

number of cases. After the more acute stages have passed, zinc oxide ointment serves a useful purpose. If there is deep-seated inflammation with vascular changes or necrosis, general antiseptic principles are to be applied, and unfortunately must at times be long persisted in.

Unquestionably these effects may be prevented in most instances by careful technique. I believe, however, that in some instances a dermatitis hastens the cure and is therefore desirable; that is to say, that when the treatment is forced to the point of producing a dermatitis, a cure is generally more rapid and certain.

To avoid "burns" the tube should be probably not less than six inches from the skin, and the exposures of short duration (five to ten minutes). The static machine seems no less likely than the coil to cause such dermatitis. Exposure should cease when the patient announces a tingling or burning in the irradiated parts. No sign of dermatitis may show itself for a week or more after this, while if sittings are persisted in, redness and pain may develop within a few days.

D. calorica.—Picric acid is one of the newest remedies for burns and scalds, being used chiefly in one-per-cent. watery solution. For superficial sunburn it has been advised in saturated solution in ether or alcohol or both. The Esbach solution, containing two per cent. citric acid, is a convenient form in which to apply the drug.

D. medicamentosa.—Achard and Clerk [53] saw picric acid applied to a slight burn cause a scarlatiniform rash of the whole body, with swelling and vesiculation of the face and intense itching. There was desquamation after fourteen days. Several cases of boric-acid dermatitis have been reported. Grumpet [54] observed marked dryness of the skin after intestinal irrigations. Redness of the skin and albuminuria were observed by Wild [55] after ingestion of eighty grains of boric acid within twenty-four hours. Uræmia being the chief danger in long-continued administration, the kidneys must be watched.

Milian [56] produced purpura of the mouth at will by large doses of potassium iodide. Exalgin was seen by Linossier [57] to produce brilliant red papular areas and later desquamation and bullæ. There were erythematous patches on the gums and a burning pain the entire length of the alimentary canal. Primula dermatitis, due to contact with Primula abconica, which was described by White, of Boston, in 1889, has been observed by Heuss.[58] He says that chronic inflammation from this cause is rare. The irritating agent is the fine hair on the under surface of the leaves which causes more or less inflammation of the hands and face, with production of papules and vesicles.

D. venenata, due to contact with wet leaves of common ivy (Hedera helix) is reported by Munro.[59] The eruption bore a resemblance to *herpes zoster.*

A vegetative dermatitis has been described by Purin,[60] deep red

patches, rounded, limited, and distinctly elevated, with vegetating surface, occurred upon otherwise healthy infants. Examination showed staphylococci, a bacillus, and a small coccus.

Dermatitis herpetiformis.—Duhring's disease has during recent years continued to excite considerable interest. Hardouin [60] finds that the attack always coincides with a decided increase in the elimination of urea, and that there is a constant relationship between the various outbreaks and the excretion of urea. Eosinophilia, while sometimes absent, is found in other bullous conditions, so that the part it plays in the affection cannot be said to be definitely settled. In a case of Brown's [61] the eosinophiles became less numerous as the skin improved. Leredde [62] says that to be of positive worth as a factor, eosinophiles in the blood and their excretion by the skin should be coexisting conditions. Albumin seemed to be an etiological factor in a case of Abraham's,[63] and pregnancy in another. The supposition that the disease is uncommon in childhood is refuted by several cases recently reported. In one by Rousell, [64] phimosis seemed the sole causative factor. Brocq [65] reports a case in which the affected areas became cicatricial with the development of small epidermic cysts. Static electricity was found beneficial and has been used in other cases to relieve pruritus. Arsenic in rather large dose has given good results, while salophen, salol, antipyrin, have all seemed to be of service. Dry powdered sulphur externally is sometimes beneficial.

Squamous Affections.

Psoriasis.—The view that psoriasis is to be classed among the parasitic affections has been gaining steadily during recent years. Munro,[66] while not able to find any microorganism, concludes that the disease is not due to rise of horny epidermis as hitherto supposed, the abnormal keratinization being secondary to miliary abscesses of the epidermis situated almost upon the surface of the corneous layer. Gottheil [67] treats obstinate cases with subcutaneous injections of a one-per-cent. solution of arsenate of sodium. As much as thirty drops may be administered every second day without ill effect. A number of obstinate cases have been reported benefited by radiotherapy, and I have myself shown a patient in whom this treatment has produced marked effect. Eugallol dissolved in acetone has been used by Goldschmidt.[68] After fifteen to thirty minutes a zinc paste is applied. Its use upon the face is prevented by the blackness which it causes. The method would seem to be too tedious for extensive eruptions. Cacodylic acid, being less toxic than other arsenical preparations, can be given in large dose, and hypodermically is painless, by which method 0.40 (gr. vi.) may be given daily, according to Danlos.[69] Neuman has injected cacodylate of sodium with some benefit.

Pityriasis rosea.—It has been found by Hallmann [70] that the changes in the macular stage of pityriasis rosea are chiefly in the cutis. There is decided broadening in the superficial vascular network and a perivascular cell infiltrate in the papillary body and subpapillary layer, with œdema of the upper portion of the chorium. These changes are more pronounced in the later stages. There is proliferation of the prickle-cell layer, especially in the interpapillary portions. Later in the process small vesicles form beneath the corneous layer, which in time is cast off. The disease seems to begin in the cutis proper, extending later to the different layers of the epithelium.

Papular Affections.

Lichen planus.—One of the most interesting things in connection with lichen planus is the formation of bullæ when arsenic has not been administered, to which I, amongst others, have called attention in a paper read before the American Dermatological Association in 1901.

Hallopeau and Lesourd [71] mention a case in which the lesions on the palms were deep-seated vesicles. Mackenzie [72] mentions bullæ forming under the thickened epidermis of the foot sole. Bettmann [73] confirms these observations with a new case of his own, and believes that in some cases at least a special variety of the affection is present. In commenting upon this case, which the author calls lichen ruber pemphigoides, Duhring and Hartzell accept the conclusions, while admitting that in America vesicular and bullous lesions in lichen are very rare.

Orbaek [74] reports atrophic changes observed in certain patches. Of late years more cases in children have been reported than formerly. Edowes [75] reports one in a child of four and one-half years.

Hallopeau and Gardner [76] report a case of lichen planus in which the lesion was band-like and circinate, but the scattered lesions were quite typical.

The treatment of lichen planus is still essentially the same, arsenic being regarded as almost a specific. Lusk has treated a number of cases with mercury with good results, drawing the faulty conclusion that lichen planus is a syphilide.

A peculiar form of ringed eruption on the back of the hand is mentioned by Galloway,[77] resembling both the annular form of lichen planus and lupus erythematosus. An infiltration of new cells was found similar to those in certain chronic inflammatory conditions of the cutis.

L. scrofulosorum.—Gilchrist [78] describes an instance in a negro, being probably the first on record. The microscope showed tuberculous structure well marked, but no bacilli were found.

Lichenification.—This is the designation given by the French to a peculiar dry infiltrated condition of the skin, due to constant scratching for the relief of localized pruritic conditions, and is often found as a complication of eczema. It is somewhat similar to the "eczematization" by which Besnier designates eczematous symptoms complicating such irritable conditions as prurigo. It differs somewhat from the eczematization of Sabouraud.

Pityriasis rubra pilaris.—Heidingsfeld,[79] making a pathological study of a case described by Ravogli in the same paper, refutes the idea advanced by Kaposi, that pathologically the condition is identical with lichen ruber. He maintains that pityriasis rubra pilaris is essentially a disease of the hair follicles, with hyperkeratinization about the hairs and within the follicles. The follicles are at times found raised from their beds and extruded upon the skin surface, covered with the stratum corneum alone. Cellular infiltration is limited to the subpapillary layer. Elastic fibres are here also in excess. In lichen ruber, on the other hand, the process is papular with extensive infiltration, involving perhaps four or five adjacent papillæ, and the subpapillary layer is not infiltrated.

Bullous Affections.

Pemphigus.—The class of pemphigus is becoming more and more restricted by the exclusion of dermatitis herpetiformis, impetigo contagiosa, pompholyx, dermatitis medicamentosa, the several hydroas, the bullous form of erythema multiforme, and bullous syphilides. Wallach[80] describes an organism similar to the bacillus of pseudodiphtheria found in the vessels and blood.

Von Michael[81] describes pemphigus of the conjunctiva, which occurs also in the foliaceous form, usually causing contracting cicatrization and ankyloblepharon with corneal implication. The cornea may become clouded, dry, lustreless, and desquamate, leading to xerophthalmos. A rather noteworthy case from the therapeutic side is noted by Van Harlingen;[82] pemphigus of severe type in a boy of five years was successfully treated by opening the bullæ and applying lint wet with 1: 2,000 mercuric bichloride solution. In a relapse six months later, cure was effected within twenty-four hours with the same treatment. In chronic pemphigus of the mouth, Bryan[83] claims that arsenic is curative.

P. vegetans.—The first case reported in this country was described in 1891 at a meeting of the American Dermatological Association.[84] The first symptoms are ill defined with malaise, languor, and later the appearance of ill-developed bullæ, appearing as white patches upon the mucous membrane of the mouth. Excoriated patches soon take the place of these lesions, rendering mastication painful and inter-

fering with nutrition. Coincidentally or later appear bullæ and lesions, especially about the mouth, and the vulva in women, which soon take on vegetating features resembling at times condylomata and giving rise to a suspicion of lues.

As is well known, the affection proves fatal in about nine months. Mracek,[86] however, saw a woman whose first symptoms had begun seven and one-half years before, and who for three years was free from eruption. Subsequently, furrows appeared, covered with verrucoid vegetations resembling those of acanthosis nigricans. Under prolonged use of arsenic the attending pigmentation was greatly diminished.

P. neonatorum.—Many of the reported cases in early infancy, especially when occurring in several children in a family or institution, must be carefully differentiated from impetigo contagiosa.

Block[87] recognizes a benign and a malignant form. The latter resembles P. foliaceus and also somewhat Ritter's D. exfoliativa, and, like it, almost always ends fatally. It appears to be a generalized infection usually depending upon streptococci; it is contagious, and its spread is often due to transfer by a midwife. Matzenauer[87] finds, in common with most observers, that the condition is almost identical with impetigo, and that it has its histological seat between the mucous and horny layers. He finds cocci of similar appearance in both affections. Glasson[88] opened the individual bullæ in an infant three days old and applied a simple antiseptic. Internally, Fowler's solution in one-minim dose was administered; recovery took place in seven weeks.

Pustular Affections.

Impetigo is a term which should be retained because of its convenience in conveying to the mind a clinical picture of more or less definite outline, though in the past it has been applied to a variety of pustular affections of probably different origin. The tendency of the French school seems to be to make of impetigo a distinct affection which occurs under several forms, but each having a definite cause. Most cases show a mixed infection of streptococci and staphylococci. Unfortunately, till now attempts to distinguish with absolute certainty the organisms from those of pus in other affections have not been successful. Engmann[89] believes that the bullous form of impetigo is very prevalent in St. Louis. In seven cases he obtained pure cultures of staphylococcus aureus.

Inoculations resulted in bullæ similar to those in the original case, and from these the staphylococcus was again cultivated. Sabouraud[90] distinguishes the impetigo of Tilbury Fox from that of Bockhart, which occurs as rounded pustules about a hair and containing yellow pus from the first. The one may complicate the other. Ecthyma

bears the same relation to the first as folliculitis bears to the second. Fehleisen's streptococcus is constantly present in the first. In Bockhart's impetigo the staphylococcus aureus of Rosenbach is found. Gilchrist[91] found the streptococcus pyogenes in each of seventeen cases, while in ten it was the only organism present.

Scholtz and Raab[92] conclude that under special conditions, as those produced by scratching, staphylococci and streptococci usually act in association, but under other especially favorable conditions either may act alone.

Impetigo adenosa.—Under this term Aronstam[93] describes a type of impetigo attended with fever and swollen lymphatic nodes, pains in the joints, vomiting, chills, and at times convulsive movements. A bright scarlet zone surrounded the pustules. After rupture and crusting a raised border of mahogany tint was surrounded by a deep red area.

In therapy Scholtz[94] advises:

℞ Sulph. præcip 10.0
Pulv. zinci oxidi,
Pulv. amyli ..... āā 25.0
Glycerini,
Aq. destillat..... 25.0
M. Shake and apply after crusts are removed.

Sycosis.

The chief advance to be noted in this affection is its curability by *x*-radiation. A number of obstinate instances have been reported upon favorably. In inveterate sycosis of the upper lip, Hodara[95] advises the following:

℞ Sulph. 10.0
Zinci oxidi 20.0
Sacchari..... 20.0
Glycerini 10.0
Petrolati,
Lanolini .... āā 20.0
M. Sig.: To be applied thickly night and morning.

After pustulation has ceased apply at night only; a simple oil is to be applied in the daytime. The most essential thing in the treatment of this most obstinate affection is to relieve or cure the usually concomitant one within the nares—chronic catarrh or ozæna. Deep scarification is advised by Crocker.[96]

Diseases of the Hair and Nails.

Loss of hair was discussed in a paper by Jackson,[97] who finds that men become bald more frequently than women, while no influence is exerted by the married or single state. An intellectual and indoor

life, especially when accompanied by worry or nervous strain, is a predisposing if not an exciting cause. Loss occurs with great frequency in the decades following the thirtieth year. The chief predisposing cause is heredity. All diseases of lowered nutrition are predisposing and at times determining causes. Some disease of the scalp or hair itself is the exciting cause in ninety per cent. of the cases. In the matter of treatment, precipitated sulphur is advised, in strength of ten per cent. in a good cold cream, with or without salicylic acid (three to five per cent.), or extract of jaborandi (ʒ i. to ℥ i.). Dr. Bronson's formula is well spoken of: Ammoniated mercury gr. xx., calomel gr. xl., vaselin ℥ i.

The author believes there is no permanent cure for dandruff, and relapses must be expected. Massage is looked upon as the only remedy for stimulating the hair growth. Dr. Ravogli[98] finds dry seborrhœa, sometimes seborrhœa fluens, and occasionally hyperidrosis, the cause of most baldness. He prescribes for the latter forms:

℞ Formaldehyd..... ʒ i.-ij.
Glycerin..... ʒ ij.
Aq. coloniensis,
Sps. vini rect.....āā ℥ iij.

Hypertrichosis.—An interesting discovery in connection with *x*-ray work is the accidental alopecia occasionally produced and the treatment of superfluous hair to which this has led. Varying success has attended the method, but unless the suggestion made by Freund[99] is carried out, to renew the exposures every six weeks after the hair has fallen, the hair will often grow again.

The present writer sees no especial advantages in the ray over electrolysis in the vast majority of cases.

Green hair is found in those who work in copper, along with other symptoms of poisoning. Lewin[100] found it in eight workmen out of three hundred examined. Whether the metal is deposited within the hair or on its surface is a question which he leaves unsettled.

Monilethrix.—The most plausible theory of the origin of this peculiar nodose or beaded condition of the hair leading to baldness is that it is a trophoneurosis, according to Ruggles[101] who reported a case in which the legs were affected, the hair showing alternate enlargement and contraction of the shaft. He reports that McCall Anderson found fourteen cases in five generations, and Sabouraud seventeen cases in five generations.

Benign Neoplasms.

Lupus erythematosus has been studied by Fordyce and Holder,[102] who find that pathologically the disease is one showing raised capillary pressure with characteristic phenomena of obstructional infiltration.

Bacilli were not found, and they do not regard it as a tuberculosis. Roth,[103] however, thinks the affection must be regarded as of tuberculous origin. Rona[104] holds the same view. Out of 53 cases, 25 gave a vague history of family tuberculosis. Among the recent forms of treatment, the most important probably is that by phototherapy, including radiotherapy, although the results do not appear so positive as those in lupus vulgaris, while the tendency to recurrence is increased. Leredde[105] reports the results in 11 rebellious cases treated by phototherapy. Three were cured, 2 benefited, 4 improved, and 2 were not.

The method is one which should be used only with great care, and is most appropriate for the obstinate and extensive cases not influenced by other known measures. Brocq advises a collodion dressing made with salicylic acid 1 part, pyrogallol 3, flexible collodion 40 parts. Whitehouse[106] has had some benefit from iodoform in one-grain doses after each meal. Hans Hebra advises moistening the parts frequently with absolute alcohol, ether, and peppermint water. Others have spoken well of absolute alcohol containing some menthol. It should be applied at frequent intervals and allowed to evaporate. Hutchinson reports a cure from pure carbolic acid painted on once or twice per week.

On account of its rarity (four similar cases only appearing in literature), it is worth recording Pringle's case of multiple epithelioma developing upon L. erythematosus. The lesions were upon the scalp of a woman aged thirty-six years.

Molluscum contagiosum.—The rarity of the location makes the report by Balzer and Alquier,[107] of a lesion upon the sole of the foot of a boy, worthy of note. A tumor had existed for about eight months, increasing in size in spite of two treatments by curettage. Contrasting with this is the case of Hallopeau[108] in which the lesions were so closely packed in places as to resemble clusters of grapes. Abraham[109] records molluscum within the mouth resembling leucoplakia. Kaposi's treatment for the disseminated forms with numerous lesions includes washing with green soap and applications of salicylated soap plaster and sulphur ointment.

Rhinoscleroma.—In the histology of this affection, v. Marschalko[110] finds that the Mikulicz cells are to be regarded as specific elements, being cells which have undergone a degeneration of special nature by reason of the presence and action of the bacteria of rhinoscleroma, and constituting changes very similar to the lepra cells. Rona[111] reports that rhinoscleroma is endemic in nearly the whole of Hungary, where twenty-seven cases have been reported. In seven instances the lymph nodes have become invaded. In one case Huber found the bacillus in a condition of pure culture in an excised node; this was the second case in which regional metastasis in the lymph nodes was noted. Regarding

rhinoscleroma the statement is frequently made that the growth never breaks down spontaneously. I have reported a case [118] in which, after many years' duration, a tumor of slow growth spontaneously broke down in its middle portion and sloughed away. Ten years after the case first came under my observation, the central portion of the upper lip took on a dusky red color, developed considerable pain, and a beginning ulceration was attended with severe general symptoms. Within a period of two weeks a large portion of the tumor, including the soft gum and lower portion of the nose, was thrown off, leaving exposed the bones of the upper jaw and nasal septum. It is now over two years since this occurred, and I am informed the patient is still alive, though at that time her life was despaired of. It is of interest, in view of the statement so often made to the contrary, to note that Zeissl has also reported a case in which a considerable portion of the nose was destroyed in an ulcerative process. There is nothing especially new in the treatment. I have advised radiotherapy, but have not had a chance to carry it out.

Xeroderma pigmentosum.—About one hundred cases of this rare condition have been recorded in literature. The disease has usually been looked upon as fatal, though many subjects of it continue to exist with their deforming affection for many years. Herxheimer and Hildebrandt [119] record four recent observations. One patient, now forty years of age, showed the first signs of the disease ten years ago; he is still well enough to do his usual work. Two of the patients were brother and sister, both being attacked in early childhood. Malignant growths developed until puberty was reached, and after thorough removal remained away. The brother had two healthy children. The author's conclusions are that if the patient can be tided over the period at which malignancy shows a tendency to cease, an inevitably fatal issue need not be anticipated. In the matter of treatment, the *x*-ray has come in apparently to fill a much-needed therapeutical requirement, since the physician has felt himself almost powerless to cope with the disease, being restricted to an alleviation of symptoms and a destruction of malignant neoplasms.

I have now under treatment a boy of fifteen years, who showed the first manifestations of the affection three years ago. The numerous epitheliomatous lesions upon the face have disappeared under the *x*-irradiation, and the eyes, whose globes are both affected—one to the extent of total destruction of sight upon this side—are improving, and I have strong hope of saving the less affected globe. It is of interest to note that a younger brother, now six years of age, presents an intense lentigo of the face which he is said always to have had. I have no doubt that unless treated by the *x*-ray this will also develop evidence of malignancy. It is noteworthy that this affection, which depends

in part upon the action of light, is beneficially influenced by a form of light treatment.

Hydroa puerorum, which like xeroderma pigmentosum tends to grow better about the age of puberty, would in all likelihood receive some benefit from radiotherapy.

Pruritus.—Pruritus as a neurosis has been written upon by several authors during the past few years, the chief advances having to do with therapy. Besides internal tonics, including hypophosphites, arsenic, cod-liver oil, etc., Monroe [114] advises entire abstinence from alcohol. He finds that when the skin is dry and hot, tarry preparations, either as ointments or lotions, give great relief. In other conditions spirit of camphor and ichthyol give relief. The electric souffle applied for fifteen minutes is recommended by Morell.[115] In localized pruritus in women at the menopause, Lieutaud [116] recommends an ointment containing gr. iiss. veratrine to the ounce of lard. In generalized pruritus he gives the drug in pill form, gr. $\frac{1}{180}$, once a day, gradually increased to six times. In pruritus ani and scroti, Arnison [117] uses carbolized soft soap, to be rubbed in freely at night and allowed to remain for one hour. Andrews [118] recommends hot compresses renewed every two minutes for anal itching, and extremely hot sitz baths for pruritus ani; he finds dry hot air efficacious in many forms. Leredde [119] finds in localized forms methyl salicylate, one part to twenty each of zinc oxide and vaselin, acts well. Douching the spine is recommended by Besnier.[120] He also points out the importance of avoiding food which may undergo fermentation. For their constitutional effect, he recommends such drugs as valerian, musk, and carbolic acid. As an internal antiseptic Parrisot [121] gives benzonaphthol and an exclusive milk diet, especially in old people.

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DISEASES OF
THE NOSE, PHARYNX, AND LARYNX.

BY

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NEW YORK.

THE two decades previous to 1890 were emphatically the pioneer age of progress in rhinology and laryngology. From scattered publications dealing mainly and in a general and indefinite sense with "catarrh," there has been developed a most voluminous literature reduced to orderly arrangement and overwhelming one with the richness of its clinical material. A new specialty has been created from which have come notable solutions of some of the problems of internal medicine. Rhinology and laryngology have amply justified their *raison d'être.*

The pioneer work in this field of medical science was carried out along broad lines and with generous impulses. The anatomy of the upper air tract was carefully studied and its physiology carefully elaborated. The catarrh question was vigorously attacked and out of the maze of clinical observations were elaborated a systematic classification of disease, a well-ordered symptomatology, a logical differentiation of the various conditions found, and a therapy, medical and surgical, based on common sense. Naturally in its zeal the profession went to many extremes, some of which were soon found to be unjustifiable and many of which now appear almost ludicrous. These pioneers were, however, men who had a groundwork of knowledge of general medicine and surgery, and the foundations they laid were strong and deep.

For a long time the most vexing of the problems presented was that of pathology. But order gradually emerged from chaos, and if we were asked to name the two most important features of the development in rhinology and laryngology for the last ten, and especially for the last five years, we would unhesitatingly reply, the clarification of pathology and a reaction from extreme surgical measures. The settlers have followed upon the track of the pioneers.

It cannot be said that the last five years have witnessed any startling changes in this branch of medicine. In addition to the points named above, there has been a greater care in observation and a far greater respect for the integrity of intranasal and intralaryngeal tissues. Best of all, the work has been largely rescued from the charlatanry formed around it.

The aim of this brief chapter is to traverse the ground in the same general order in which the subject was treated in volume VI. of this work, calling attention to such matters as seem worthy of special mention.

THE NOSE.

Nothing need be said concerning methods of examination and no new instruments of special value have been devised. We have received a most valuable contribution to our pharmacopœia in the suprarenal extract, now commonly employed in the shape of a 1–1,000 solution of its active principle, adrenalin, in saline solution, preserved by chloretone. It is not too much to say that in its value to the rhinologist this remedy is second only to cocaine. Its hæmostatic properties are little short of marvellous. It acts on the unstriped muscular fibres of the vessel walls, whereas cocaine produces its constringing effects through the vasomotor nerves. At first a saccharated extract of the suprarenal body was used, freshly prepared in distilled water, and this may still serve if the adrenalin is not at hand.

It is a brownish powder with the general appearance and odor of powdered pepsin. A certain quantity, say fifteen grains, may be added to a drachm of sterile water or a two-per-cent. solution of resorcin in water and well shaken. The resulting mixture is applied to the nasal mucosa on cotton pledgets or by spray. In such an emergency as nosebleed, the powder may be directly applied. A more elegant preparation results from allowing the mixture to stand for twenty-four hours, shaking frequently, and then filtering. The product is a clear solution of a port-wine color. The adrenalin solution obviates all such troublesome preparation. It may be diluted to 1–5,000 or even to a weaker strength and still promptly manifest its power. It is not of itself anæsthetic but it may be used in the same solution with cocaine. We prefer to use the remedies separately, the cocaine preceding. The adrenalin can be repeatedly sterilized without any impairment of its properties. The mucosa is speedily blanched and with the two remedies we can render the operative field anæsthetic and bloodless, in other words can obtain ideal conditions for operating quickly, safely, and agreeably.

The discussion of the physiological office of the adrenalin in the normal body is beyond the province of this chapter. Suffice it to say

that when absorbed into the circulation it raises the blood pressure and stimulates a flagging heart. For a long time it was supposed that it was so changed in its passage through the gastroenteric canal that when swallowed its effects could not be produced, and we may add that testimony on this point is still somewhat conflicting, but the results obtained in many cases of hay fever from internal administration seem to prove the fact that it is absorbed unchanged.

Obviously after the use of such a powerful astringent agent there must come a reaction, and the question has been much discussed as to whether secondary hemorrhage in operations with adrenalin is more common than in the period preceding its use. Testimony on this point has been carefully collated by Hopkins of Springfield, Mass. (Transactions of the American Laryngological Association, 1900). As usual, it is conflicting, but Hopkins believes that bleeding is more frequent than formerly, and says that the nasal fossæ should be carefully packed after every operation; and, furthermore, that such packing should be saturated with an astringent. For the latter purpose many prefer the acetotartrate of alum in fifteen-per-cent. watery solution. Some writers advise the placing, after operation, of a solution of the adrenalin in the hands of the patient so that a reapplication may be made on the first appearance of bleeding. The writer of this chapter employs packing for the first twenty-four hours, placing against the raw surface a bit of sterilized rubber tissue and against this a firm plug of sterile gauze. When the packing is removed, the rubber tissue can be carefully lifted away from the cut surface without tearing open any of the small vessels and so starting up the bleeding afresh. The packing is not replaced but the nostril is thoroughly cleansed and insufflated with an antiseptic powder. In addition, the patient wears for a few days a pledget of cotton in the nose to filter out the dust of the inspired air.

An occasional disadvantage of adrenalin and one that cannot be foreseen is that it may produce by its violent reaction in non-operative cases a severe coryza with sneezing. This may happen when the remedy has been used to prevent an oncoming cold in the head, so that the last state of the case is worse than the first.

Very recently several cases have been reported of œdema of the palate, pharynx, and epiglottis following the use of the remedy in the throat. So far as is known, these cases have presented no constitutional symptoms. Scarification has been followed by relief. Theoretically adrenalin is indicated in the incipient stage of all acute catarrhs when circumstances permit of its direct application. It will frequently abort a commencing laryngitis. It may act equally well in the pharynx, though patients often complain of a disagreeable dryness.

In spite of these drawbacks, however, the consensus of opinion is that the remedy is second only to cocaine in its beneficial results in nose and throat practice. Like all remedies, it should be used with prudence, and in spite of every precaution untoward effects will sometimes occur.

Local Anæsthetics.—Nothing has been presented to supersede cocaine. Various modifications of the remedy have been made, notably phenate of cocaine, which must be used in somewhat stronger solution than the simple cocaine. It is, however, less toxic. Tropococaine, an alkaloid obtained from Java coca, is another substitute but has never come into general use. Eucaine ("a" or "b") has been proposed. A combination of much value has been suggested by Gray. He prepares two solutions. The first consists of muriate of cocaine, twenty per cent. in rectified spirit; the second of "B"-eucaine, twenty per cent. in aniline oil. Some of the eucaine does not dissolve in solutions of this strength and the bottle should therefore be well shaken at the time of using. Ten minims of each solution are mixed, the resulting fluid becoming clear in a few minutes. Gray admits that this mixture is somewhat burning in the nose and throat, but claims that this disadvantage is more than compensated for by the deeper anæsthesia obtained and especially by the absence of symptoms of cocaine intoxication. For application to the nasal mucosa he prefers a strip of gauze to cotton. The twenty minims prepared as above stated are quite sufficient for the painless excision of tonsils, removal of septal spurs, cauterization, etc. In applying the remedy the effects are greatly enhanced if it be rubbed for a few seconds over the operative field. A peculiar effect noted in one or two instances, referable probably to the aniline element, was a peculiar blueness of the lips, due, it was supposed, to the conversion of the oxyhæmoglobin of the blood into methæmoglobin.

Still another plan, and one in the experience of the writer of great value, is that proposed by Wingrave. It is a combination of a five-per-cent. solution of cocaine muriate with two per cent. of sodium sulphate. The addition of the neutral sodium salt decidedly increases the effectiveness of the cocaine, partly by reason of its penetrating power and partly owing to its solvent action upon the globulins and other proteids occurring in the secretions. As cocaine is an expensive remedy, an additional advantage is gained by the lessening of the amount required.

Still another class of remedies used for the same general purpose is represented by guaiacol, which often, though not always, exerts surprising anæsthetic effects. It may be dissolved in alcohol or in olive oil as the latter is less irritating to the tissues. Guaiacol does not readily mix with olive oil, even the purest. So the latter must be

cleared of its resinoids, albuminous and coloring matters by zinc sulphate and from its fatty acids by absolute alcohol. The following mode of preparation has been found suitable. To a given weight of oil, ten per cent., by weight, of dried zinc sulphate is added and the mixture heated over a water-bath for one hour. It is then filtered and twelve and one-half per cent., by weight, of absolute alcohol is added. It is shaken occasionally for a few days and then decanted. The result is a clear, limpid mixture with which olive oil, say five per cent., mixes readily. Its action is much slower than that of cocaine, as we must wait fifteen or twenty minutes for complete absorption. It has no advantages over cocaine, but is a fairly reliable resource if for any reason the use of cocaine is inadmissible.

Another valuable remedy is orthoform, a compound known in synthetic chemistry as the methyl ester of para-amido-meta-oxybenzoic acid. It is a white crystalline powder without odor or taste and very slowly soluble in water, prolonged contact with the tissues being thus effected. It is anæsthetic only when in contact with raw surfaces presenting exposed nerve endings. As used in the upper air tract no evidences of toxicity have been reported, though severe dermatitis has been noted from its extensive application over wound surfaces. Its chief fields of usefulness seem to be in cases of painful ulcerations about the mouth and fauces; over the stumps of tonsils removed by cautery, and especially in the painful swallowing of laryngeal tuberculosis and malignant disease. It can be insufflated in powder or applied in an emulsion with white of egg and oil of wintergreen. Freudenthal suggests the following formula: Menthol 10, almond oil 30, yolks of two eggs, orthoform 12, and water up to 100.

In view of the insolubility of the remedy a chloride has been prepared and is sold under the name of "nirvanin." In two-per-cent. strength in a sterile salt solution it can be employed much as is cocaine for injection into the tissues, but its anæsthetic effect under these circumstances is not so pronounced as is that of the older and better-known remedy.

Intranasal Packing.—Whenever packing is necessary, a valuable device exists in the "Bernays' sponge," devised by Bernays of St. Louis and introduced into rhinological practice by Simpson of New York. It is made of prepared cotton fibre subjected to very high pressure and then cut into discs or splints adapted to the shape of the nasal chambers. In its natural condition it is quite thin, but upon absorption of blood or moisture of any kind it rapidly swells and thus forms an efficient plug. It is sterilized and can easily be retained without harm for twenty-four hours. To the side in contact with the raw surface of tissue can be cemented, by means of iodoform collodion, a small strip of gutta-percha. Thus a smooth surface is presented,

and on the removal of the sponge there is no re-opening of the mouths of small vessels.

Nasal Physiology.—While no new facts have been discovered, all writers call attention to the function of the nose as a respiratory organ, and many pleas have been made for conservatism in procedures tending to destroy the nasal mucosa. Parker (*Journal of Laryngology*, July, 1901, p. 345) has performed an interesting series of experiments to determine the course of the inspiratory and expiratory currents. For the former he had the patient inhale lycopodium powder and noted the areas of deposit in the nasal fossæ; for the latter the patient exhaled through the nose the smoke of a cigarette. Parker notes the following results: In a normal nose the inspired air traverses the middle and upper portion of the cavity; its course is therefore impeded by septal spurs and deviations, forward and upward enlargements of the inferior turbinates, enlargements of the middle turbinates, polyps, nasopharyngeal growths, and hypertrophies from the vault; the expired air traverses especially the inferior meatus and is therefore impeded by posterior hypertrophies of the inferior turbinates—in fact, by any cause obstructing this passage.

Bacteriology of the Nose.—This question has been extensively studied during the last five years. In its consideration it has been found that we must carefully discriminate between the vestibule and the nasal interior. The former swarms with bacteria, but the latter is relatively free therefrom. This distinction is assignable to three factors: (1st) the movement of the ciliated epithelium; (2d) the inhibitory power on germ growth of the nasal mucus; and (3d) the phagocytic power of the leucocytes. With reference to the second factor, it may be said that the latest experiments deny to nasal mucus a distinctly bactericidal power; it is merely inhibitory. Most authorities agree that the nose contains some, though but few, pathogenic bacteria. This being the case, it is always desirable to secure as nearly an aseptic condition as possible before we operate. The vestibule should be carefully cleansed and the side operated on should be closed with a cotton filter. A theoretical objection to plugging in this connection may be mentioned, namely, that it tends to retain nasal secretions. Nasal wounds do not heal by first intention owing to the presence of bacteria, which plugging would naturally tend to retain in the fossæ. Iglauer ascribes secondary hemorrhage to the same cause, and as well, post-operative fever.

Of cultures made by Thompson and Hewlett from the nasal interior, eighty-four per cent. remained absolutely sterile. They have also shown that if a culture is made on the septum it is rapidly removed by the action of the ciliated epithelium, and cultures made from the site of inoculation two hours later have remained sterile.

Another interesting question is the relation of the nose to general tuberculous infection. Many bacilli must there be arrested, and we know from experience that the nasal mucosa is better able to withstand this particular form of infection than is any other portion of the respiratory tract. Hence the necessity of maintaining the normal patency of the nose. Deficiency in this respect eventually means deficient oxygenation of the blood, a thing to be most carefully avoided in a patient disposed to tuberculous trouble. Careful inspection of the nose should be made in every case of tuberculosis coming under observation, and any remedial measures indicated should be at once instituted.

Nasal Neuroses.—On this question there has been somewhat of a reaction from the extreme views of an earlier period. On the other hand, careful observation has established a definite relationship between intranasal states and eye conditions, notably those of asthenopia of the ciliary and external muscles. This relationship is attributable to pressure existing in the region of the middle turbinate, the adjacent septum, and the ethmoid sinuses. Classical articles have also appeared from Fliess and J. N. Mackenzie on the relations between the nose and the genital organs. An attempt has been made to isolate a "genital area" on the nasal mucosa. Fliess takes a somewhat extreme position, relating a number of cures of dysmenorrhœa (only that form in which pain persists after the flow has been established) by cauterization of the genital area. He believes that labor pains are influenced in the same manner, going so far as to say that the nose "is a station on the route travelled by the stimuli on their way to the brain." Not all pains take this route, but only those corresponding to the excitation of certain spinal segments. Other observers claim to have relieved menstrual pains by cocainization of the genital areas.

Rhinitis.—Little new has been brought forward concerning hypertrophic rhinitis, though new plans of treatment have been proposed. Several authors advocate the injection into the hypertrophied turbinated tissue of a ten-per-cent. solution of zinc chloride, but this method applies only to those cases in which the enlargement is of the soft variety. Goldstein has suggested an ingenious method of submucous cauterization performed by passing a fine trocar and cannula into the tissue, withdrawing the trocar and replacing it with a probe on the end of which is fused chromic acid. The whole apparatus is then withdrawn, leaving a cauterized tract along the channel of exit. Delavan suggests the puncture of the tissue with a very fine blade, which is swept around so as to destroy the vessels. A clot results, which by its subsequent contraction leads to a shrinkage of the area involved. For the removal of large masses of tissue the snare and scissors still hold the preference. The middle turbinate has been more

boldly attacked than formerly, especially in cases in which there has been obstructed nasal drainage. But all observers agree that cauterization in this region is attended with great risks, owing to the proximity of vital structures, which are in such intimate relation with the lymphatics of the soft parts covering the bones.

Several papers of interest have appeared on the etiology of atrophic rhinitis, notably those of Grosheintz and Meisser (*Arch. f. Laryngol.*, vol. viii.). Their main contention is that the disease depends on the form of the skull and nasal passages. Grosheintz measures the skull from the frontonasal suture to the alveolar border of the upper maxilla between the middle incisor teeth for length, and between the malar eminences for width. He then multiplies the length by 100 and divides by the width. The resultant he styles the "upper facial index." In thirty-nine out of forty cases thus measured in German Switzerland, Meisser found an index of 50 or less. In general the smaller the index the larger was the number of cases of atrophic rhinitis with ozæna. He offers the following conclusions:

1. Fetid atrophic rhinitis most commonly occurs in patients with an upper facial index below 50; that is, the broad-faced type.

2. In unilateral cases the epithelium of the apparently sound side, at least in the region of the middle turbinate, has undergone a metamorphosis.

3. For the existence of the clinical picture of fetid atrophic rhinitis we must assume two factors: (1st) epithelial metaplasia of the nasal mucosa, and (2d) wide nasal fossæ (chamæprosopia). A certain confirmatory evidence of the truth of Meisser's theories is found in the results of clinical observation in the Eastern United States, for the majority of cases of marked atrophic rhinitis is seen in foreigners who present the facial characteristic indicated above. Of course the affection (generally, however, in minor degree) is found in Americans who regularly present the higher index, *i.e.*, over 50.

Coinciding in general with the foregoing propositions, Gerber attributes an etiological relation to a retarded development of the nasal framework; that is, he carries the process merely one step farther back.

Less has been heard during the last few years concerning the bacteriology of this affection. Several microorganisms have been exploited as the exciting factor, but upon this point there is far from a unanimity among the different observers. A noteworthy contribution to the subject is that made by Belfanti and Della Vedova (*Arch. Ital. di Otol.*, 1896, p. 189). They claim that the disease is caused by an attenuated type of diphtheria bacilli and not by the B. mucosus ozænæ, the microorganism which has the greatest number of advocates in this respect. They instituted antitoxin treatment, and in about one-half of their cases caused a disappearance of the fetor, produced a

turgescence of the mucosa, and increased the fluidity of the nasal secretions. They used large amounts of the remedy continued over a long space of time and without any injurious constitutional or local effects. Others have repeated their therapy without any benefit whatever. It is generally believed that injections of sterilized serum alone would have accomplished the same results. The same may be said of any agent that would cause an increase of nasal secretion.

Concerning treatment in general, it may be said that persistent cleanliness continues to be the sheet-anchor. This is to be supplemented by such topical remedies as will stimulate whatever of glandular tissue that may remain. Ichthyol in gradually increasing strength enjoys at present much popularity in this respect. Formalin has also been used. Citric acid and sugar of milk insufflated in equal parts have been shown to have a remarkable deodorizing but in no wise curative power. Cupric electrolysis has many advocates, as has also massage. It will be noted that all of these measures aim at the same end, namely, to increase the watery transudation from the tissues. None of them are curative. If they are faithfully persisted in, the patient will get into a very comfortable state, and when once that is attained a daily making of the nasal toilet will generally hold all that has been gained.

Much has been written during the last few years concerning the relation of atrophic rhinitis to sinus disease. That the latter is the cause of all cases of the former, no one contends; that it is the cause of some cases, nearly every one admits. One writer (J. E. Logan) makes a strong point for this theory in the statement that he cannot conceive how the nasal mucosa, robbed of its epithelium, stripped of its glandular tissue, and practically devoid of its blood supply except through minute channels, could maintain the excessive secretion found in the nares in atrophicr hinitis. Nobel and Lohnberg (*Berliner klinische Wochenschrift*, March 26th, 1900) found sinus disease in one or more cavities in seventy-nine out of one hundred and eleven typical cases of atrophic rhinitis with fetor and crusts. T. J. Harris well reflects the prevailing opinion in his statement (*New York Medical Journal*, October 9th, 1897, p. 519) that "focal disease, including especially disease of the accessory sinuses, while not the only cause is a very important and common one, and that as a practical conclusion for the rhinologist each case of ozæna, in addition to being treated with the proper constitutional and local measures, is to be thoroughly and repeatedly examined for evidence of such sinus involvement." Still another unique plan of treatment consists in injecting paraffin into the turbinal tissues. The technical procedure is the same as that mentioned below for the correction of nasal deformities. The idea is to build up the atrophied turbinals so as to narrow the nasal chambers in the hope that

a restoration in this respect to the normal will tend to lessen crust formation. It is evident that the injections are applicable only to those cases in which the atrophying process has come to an end; it would obviously be foolish to hope for a cure by this means if sinus disease or suppuration higher up was responsible for the intranasal changes.

Hay Fever.—Little has been advanced that increases our knowledge of the nature of this affection. An interesting therapy has been suggested—that of immunization—by giving to the patient the active principle of various substances derived from the various forms of vegetation believed to be the exciting factor of the attacks. The plan has not been carried out far enough as yet to give any decisive results. Thost believes that the excitation of the nerves of smell plays an important part and suggests that it is not so much the pollen from vegetation that causes trouble as odorous substances in the shape of ethereal oils given off under the influence of sunlight at the time of flowering of many varieties of vegetation. The adrenalin solution has been found to afford temporary relief to nasal engorgement and the remedy has been also administered internally. Testimony as to its value as thus given is as yet very conflicting. Any system of therapy must, in order to be successful, recognize the threefold factor of the affection, a systemic predisposition, an intranasal abnormality, and an exciting cause. Strangways attributes the disease to a toxin formed by fermentation of pollen in an alkaline medium, and so employs an acid douche and acids internally. For the former purpose he advises a two-fifths-per-cent. solution of acetic acid.

Nasal Hydrorrhœa.—Cases of this nature are reported from time to time, and an effort has been made to divide them into two classes, according as they indicate an intranasal condition or one due to the leakage of cerebrospinal fluid. Molinie (*Revue hebdomadaire de Laryngologie*, May 18th, 1901, p. 577) lays down the following propositions:

1. Nasal hydrorrhœa as a morbid entity no longer exists.

2. The cases fall into one of two groups determined by the rôle played by the pituitary body.

3. In the first group the nasal mucosa is the origin of the discharge under varying mechanisms and various local and general conditions.

4. In the second group the nose serves simply as the conduit for the discharge from the brain, indicating a grave intracranial condition, or from the sinuses, indicating a new growth or hydrops.

5. Whatever the origin of the discharge it is always a secondary phenomenon. Under such circumstances it is necessary to determine the cause and source of the secretion before we can formulate any rules for treatment.

Correction of Nasal Deformities.—During the last two years an ingenious plan of restoring deformed noses has been suggested. It consists of the subcutaneous injection of paraffin. Experiments on the cadaver raised to a normal body temperature show that the substance spreads itself out over the nose, forming a perfect cast of the nasal bones beneath. In operating on the living subject a weak solution of cocaine is first used and then the paraffin, one having a melting point of 130° F. being preferred. The latter is first sterilized, the air bubbles being allowed to escape and is then introduced through a sterile needle carried into the tissues well beyond the point of deformity. The paraffin remains plastic about half a minute during which time the part is moulded into a normal shape. It is found that reaction is practically nil and the time elapsed since operation has shown in several instances that a permanent result without harm may be expected.

Accessory Sinus Disease.—The advance in the study of sinus disease during the last five years has been more in the direction of perfecting operative methods than in pathology. This anatomical field has been the subject of much careful study. B. Douglass has investigated the matter of the sinuses in the wings of the sphenoid and their relation to the cavity in the body of that bone (*Laryngoscope*, February, 1901). Several authors have called attention to the frequent existence of channels of communication between the various sinuses. The obvious lesson from these researches is the necessity of a most searching examination of all the cavities in any case and the determination of the fact as to whether the antrum is the seat of the primary disease or is simply a reservoir for the drainage of the other sinuses.

The limits of translumination as a means of diagnosis have become more clearly defined. It cannot give absolutely positive evidence. Light will pass if the antrum is full of serous fluid (hydrops), but will not pass if the bones are uniformly thickened, if the cavity is filled by a solid tumor, or if the mucosa is thickened. In acute conditions the mucosa may secrete pus, but if the case is in a very early stage the membrane may not be thick enough to intercept the light. Consequently there is no opacity. But if there is a contrast between the two sides, the test becomes correspondingly valuable. The only reliable method is that of puncture (preferably under the inferior turbinate) with irrigation of the cavity. In regard to the reliability of the translumination test as applied to the frontal sinuses we can do no better than to quote the conclusions of Logan Turner on this point:

1. One or both sinuses may be absent, and when this anatomical condition exists there is opacity on one or both sides of the skull.

2. A certain proportion of healthy sinuses fails to illuminate; this may occur on one or both sides of the skull.

3. A sinus on one side of the skull may illuminate with less brilliancy than its fellow, although both are perfectly normal.

4. Many sinuses containing pus and with their mucous membrane thickened and often polypoid illuminate with considerable intensity.

Under most circumstances the patency of the natural outlets of the sinuses is a guarantee for exemption from chronic inflammation. In all cases this patency is the end first to be sought after, and if it can be attained much subsequent operative work may be avoided. In spite of very definite directions given by various authors as to just how to pass the catheter into the sinuses, the fact remains that in the majority of cases it is impossible. The judicious removal of a portion of the middle turbinate will often afford access to the infundibulum and hiatus semilunaris, thus rendering catheterization and irrigation comparatively easy.

Much attention has been given to the study of sphenoidal sinus disease. Positive diagnostic tests are still indefinite. The anterior wall of the sinus lies from three and one-half to four inches from the tip of the nose, and according to Gleitsmann, if we pass the cannula slightly upward between the septum and the middle turbinate about one-quarter of an inch higher than the inferior border of the latter and proceed to the depth named above, the end of the instrument is in the cavity.

The literature of serous accumulations within the antrum has been reviewed by W. E. Casselberry (Transactions of the American Laryngological Association, 1901) who reports two personal cases. In cases without distention or deformity the diagnosis must be made by aspiration. Translumination is somewhat indecisive, as clearness of light may be impaired without a definite shadow. This impairment, together with polyps, degeneration of the middle turbinate, indefinite supraorbital pain, and a sense of fulness in the cheek are the indications for puncture. The cases may be divided into two classes: acute with retained mucoserous secretion, and chronic with a serous discharge from the outset.

Emil Mayer reviews the literature of antral disease in young children (Transactions of the American Laryngological Association, 1901), finding recorded only about a dozen cases to which he adds one of his own. He believes the malady to be just as distinct as in later life, and not merely the expression of a caries, tuberculosis, or osteomyelitis. The symptoms in recorded cases have uniformly been fistula under the eye, usually with a purulent discharge, ectropion, foul unilateral discharge from the nose, and eroded bone. Some cases have been referable to a nasal diphtheria as proven by bacteriological tests, while some have offered no apparent cause. The usual methods of treatment are here fully applicable.

THE PHARYNX.

That *tonsillitis* is essentially an infectious disease is now generally admitted. Contagion may be conveyed in many ways. Several epidemics of non-diphtheritic inflammation have been traced to impure milk. The tonsils also serve as the portals of entrance of many infections, eventually localizing themselves in distant tissues. Normal organs doubtless play a protective rôle in the organism, but if this integrity is impaired either by overgrowth or by disease of the crypts operative measures become necessary. Scarlet fever and possibly typhoid may invade the system by this route. The primary affection may be masked by the preponderating evidence of the secondary disease. Thus, as complications of simple tonsillitis have been reported cervical phlegmon and gangrene, pleurisy, pneumonia, inflammations of abdominal organs, especially the spleen, liver, and kidneys, and inflammations of the genitals. Concerning the relations of the tonsils and pharynx to rheumatic affections there is conflicting opinion. The prevailing view may be summarized in the following propositions:

1. Tonsillitis, whether rheumatic or not, is usually the result of contamination and the absorption of irritant buccal fluids by the adjacent mucosa through the channel of the converging lymphatics.

2. In rheumatic states this contamination may be either extrinsic or intrinsic. Extrinsic agents are various microorganisms and the results of their life processes. Intrinsic contamination to buccal fluids may come through salivary or other oral glands acting as unusual channels of excretion for the poisonous substances associated with such a diathetic state as rheumatism. In either case parenchymatous tonsillitis is the expression of the poison.

3. Morbid materials, usually of the nature of chemical irritants, the results or not of microbic action, are absorbed by the faucial and buccal muosa and pass to the tonsils by the lymphatics; in such passage the lymphatic tissue becomes inflamed.

4. Accumulations in the crypts nearly always contain various germs from the mouth. The white coagulum which forms the nidus for their development is the result of the outpouring of serum and leucocytes from the turgid and irritated lymph follicles and circumferential lymph tissue. If such tension be not relieved by this leakage or by incision, suppuration follows.

A noteworthy contribution in this field during the last few years has been the establishment as a separate affection of the ulceromembranous form of tonsillitis due to the bacillus of Vincent. Contributions to the literature of the subject from continental writers have been numerous. But few American papers have appeared, notably those of Mayer, Sobel, Herrman (Transactions of the New York Acad-

emy of Medicine, Section on Laryngology, November 27th, 1901, *Laryngoscope*, vol. xi., p. 479). The affection occurs more often in adult males, though Sobel and Herrman reported a series occurring in children. It may be referred to tooth eruption, bad condition of teeth, syphilis, and lymphatism, or, at least, it has been found in connection with these various states. It may be confined to the tonsils or may appear on the tongue, gums, and cheeks. It generally assumes a chancroidal aspect with a worm-eaten floor, the edge being on a level with or slightly above the tonsillar surface. Except for the necrotic floor the ulcer has a punched-out appearance. At first the area involved seems to be covered with a membrane, but after thirty-six hours a swab applied against it apparently penetrates a cavity varying in depth from one-eighth of an inch to one inch. The color of the area may be yellowish, greenish-gray, or dirty light brown. As a rule the submaxillary glands are enlarged, less commonly the cervical. This enlargement is painless, but remains for some time after the healing of the ulcer.

Generally there are only local symptoms, fever being but slight if present. The main trouble is a pain in the throat with some difficulty in swallowing. Tonsillar ulceration alone rarely causes any fetor of the breath, but if the process has spread to any other of the sites named above fetor is present. The disease is not a dangerous one, but calls for diagnosis from diphtheria, lacunar tonsillitis, and specific disease. Several observers call attention to the fact that while smear tests from the affected area are very unreliable in diphtheria, the reverse is the case in the ulcerative tonsillitis. Here we rely mainly on the smear and very little on the culture, for up to the present time no medium has been found for the growth of the fusiform bacillus of Vincent in pure uncontaminated culture. It is claimed that the presence of the latter germ precludes the growth of the Klebs-Loeffler bacillus. From lacunar tonsillitis, the diagnosis is not difficult in typical cases of the latter, but this disease varies so much in appearance that mere inspection is often insufficient. In confluent lacunar tonsillitis we regularly expect fever, headache, and malaise, with frequently marked septic phenomena. The lesion is superficial and diffused. In the ulcerative condition fever is absent, the lesion is deeper and circumscribed. Both the lacunar and ulcerative forms may occur at the same time. From syphilis the smear test will generally differentiate the condition, though both affections may coexist. If this happens, we should treat the angina first, for mercury interferes with the healing of the local ulcerative process.

In a recent paper (*Bulletin de la Société médicale des Hôpitaux de Paris*, February 1st and March 23d, 1901) Vincent describes two forms of the affection: (1st) the diphtheroid containing the characteristic fusiform bacillus alone, and (2d) the ulceromembranous containing

both bacilli and spirilla. Herrman and Sobel describe the former as about twice as long as the Klebs-Loeffler organism, needle-shaped, pointed at the ends. They may be arranged end to end, at an acute angle, or be irregularly scattered over the field. The spirilla are long and corkscrew like with wide curves. The authors just quoted advance the following arguments in favor of the specific characters of the organism:

1. Its uniform presence in very large numbers or nearly pure culture.

2. Its gradual disappearance during the healing of the ulcer and rapid disappearance when once healing is complete.

3. The presence of so few other microorganisms.

4. The existence of instances in which the disease has been transmitted from one individual to another.

It must be added that these views as to specificity are not shared by all authors. All agree, however, as to the preferable treatment, viz., applications of silver-nitrate solutions, three to five per cent., or of Lugol's solution. The latter, while efficient, is somewhat painful. Methyl blue has also been advocated as a valuable topical agent. The area may be previously cleansed with hydrogen dioxide.

Tonsillotomy Rash.—The occurrence of a rash after ordinary tonsillotomy has been noted. The rash generally appears on the second or third day, generally lasting two or three days. It may take the form of papules, a roseola, or erythema. The favorite sites are the neck, chest, and abdomen; less frequently the face and extremities. It rapidly disappears without desquamation, but itches considerably during its continuance. Age seems to have no bearing on its occurrence. Constitutional symptoms, if present, are generally limited to a very mild fever.

The nature of the rash is a matter of doubt. Wingrave thinks it may belong to the class of eruptions which occur upon any solution of tissue continuity. Blood examinations after tonsillotomy have shown an increase in the mononuculear leucocytes, though this fact does not bear on the matter of the rash and only evidences the great disturbance of the lympoid structures incident to the operation, especially when the latter is accompanied by the removal of lymphoid tissue from the nasopharyngeal vault, the denuded areas combining to afford a large surface for the possible absorption of toxic material. Another possible explanation of the rash is that it may be a drug eruption, for many of the patients in whom it occurred had been taking the bromides or salicylates. The condition is probably analogous to the so-called "surgical scarlatina," a term introduced twenty years ago.

Tuberculosis of the Tonsil.—The literature of this subject has become quite voluminous, particularly of that phase of the question suggested by the term "latent" tuberculosis. A tuberculous tonsil does

not assume any special gross appearance. The organ is enlarged but presents to the eye no other peculiarity. The organ serves as the portal of infection for many of the cases of cervical adenitis in childhood. Dieulafoy believes that the infection of tuberculosis may be arrested in the tonsils and go no farther. Two instances of pulmonary infection have been reported (Lermoyez) which seemed to follow operations for the removal of lymphoid hypertrophy from the pharyngeal vault. Lewin has found tuberculosis in five per cent. of all adenoids examined. A conservative presentation of the subject is that of J. Wright, who after an examination of fifty-four enlarged faucial, fifty-one pharyngeal, and sixteen lingual tonsils was unable to find in any of them either tubercle bacilli or typical giant cells. Wyatt Wingrave coincides with Wright as to the absence of bacilli, and while finding giant cells does not accept their presence (in the absence of bacilli) as evidence of tubercle.

A fallacy incident to many reports on the subject is that the bacilli found under the conditions of the examination may be mere surface contamination and not the visible exponent of tuberculous infiltration. Inoculation experiments would be more conclusive but not, for the reason named, absolutely so. Some experimenters have made such inoculations, while others have not; hence the discrepancy in statistics. Tonsils are doubtless almost always infected in pulmonary disease in the adult, but are often passed over in children under seven years, because before this age the child swallows its sputa and does not expectorate.

Mycosis of the Tonsil.—Two different conditions undoubtedly exist under this appellation. In one we have merely a deposit of the leptothrix and other similar fungous organisms; in the other there is a true keratosis of the epithelium lining the tonsillar lacunæ. The two are not differentiated by mere inspection, and microscopical examination of the deposits is necessary. No better plan of treatment has been devised than the galvanocautery, but before any local measures are adopted attention should be paid to the general health. The majority of patients present departures from the normal in this respect, and many of them are cured by the regulation of the gastro-enteric tract. Semon goes so far as to say that no local treatment is necessary, and that as a rule the condition produces no symptoms whatever. From both of these propositions as stated, there will doubtless be some dissent.

THE NASOPHARYNX.

Nothing especially new can be said concerning diseases of this space or their treatment. Several observers have made a plea for more careful topical treatment, urging the use of the palate retractor so that

applications may be definitely localized and not smeared blindly over the entire area. So also the latter should be carefully scrutinized for specific localizations of ulcerative processes, persisting here after they may have healed in localities more accessible to direct treatment.

The literature of adenoid vegetations still continues voluminous. No special advances have been made in either pathology or treatment. Woodward has suggested that the deleterious effects of the condition are due not only to the mechanical blocking of the air passages, but possibly also to a toxin secreted by the adenoids. Removal does not always correct mouth breathing, and in such cases we should carefully examine the nose. The general teaching is not to irrigate or to use any solutions in the nose for a few days after operation, but to keep the oral cavity clean, the patient quiet and on soft diet. Most physicians advise general anæsthesia, though a few condemn it as unjustifiable except with unruly children, or when faucial tonsils are to be removed at the same time. In children presenting the lymphatic habitus, chloroform is certainly dangerous. The ideal combination is nitrous oxide gas, followed by ether required. Cases of hemorrhage following operation are not so few as the earlier literature would indicate. Several fatalities have been recorded and the lesson of the necessity of keeping the patient quiet after operation has been emphasized. The latter is by no means a trivial affair, though it is done so frequently. No hard-and-fast rules can be laid down as to the necessity for operation. Semon says that adenoids which do not cause any symptoms do not in his opinion require removal. Opposed to this is the extreme view of some clinicians who prophesy all sorts of dire evils either present or potential in lymphoid masses so small that they are hardly appreciable. We may safely quote from Semon's paper the advice of Talleyrand to a young diplomat about to set out on a responsible mission: "Above all, not too much zeal."

THE LARYNX.

Inflammations.—Recognition has been made of a condition called angina epiglottidea anterior. It consists of an infectious inflammation involving only the anterior surface of the cartilage where the submucous layer is abundant and becomes œdematous on slight provocation. This condition has been studied by Theisen, whose cases showed a mixed infection probably of a pneumococcic variety. Symptoms are a sudden onset, fever, dysphagia, and redness and swelling of the cartilage. Treatment consists in ice locally and internally, with a weak ichthyol spray.

Rheumatic inflammations have been carefully studied. The local condition may precede, accompany, or follow the general affection.

Local symptoms are pain, dysphagia, and tenderness on touch at the upper and outer border of the thyroid cartilage. Examination with the mirror may show nothing, or there may be redness and swelling over the cricoarytenoid joint. Cord movement is at first restricted or jerky; when effusion occurs the cord becomes fixed. Upon recovery from the acute condition ankylosis may supervene.

Tuberculosis of the Larynx.—The longed-for serum for the treatment of tuberculosis has not yet appeared, and the treatment of the condition in the larynx is mainly designed to make the patient comfortable and heal up his ulcerations so that he can swallow in comfort, even if his general disease is not checked. The plan of curetting and rubbing in lactic acid is still followed, and that of removing the infiltrated masses by double curettes and other cutting instruments has able advocates. In America the latter has not received such general advocacy as on the Continent, though in the hands of several Americans, notably Gleitsmann of New York, brilliant results have been achieved. The limitations of the class of cases to which this hardy procedure is applicable are so great that it is obviously restricted to a comparatively few out of the whole number of cases. Orthoform here finds a valuable employment, as it greatly lessens the dysphagia. The cough is often benefited by intratracheal injections made according to conventional rules. Various remedies such as phenosalyl, thiocol, etc., for topical use, have received strong advocacy, but with the usual ultimate fate, viz., a temporary popularity and then oblivion. Sendziak is inclined to attribute to orthoform not only an anæsthetic power but also a distinct antituberculous effect. The submucous injection of creosote still finds favor, and guaiacol has been used for the same purpose.

While no great progress has been made in the last five years, the interests of the patient have undoubtedly been conserved by the recognition of the fact that the laryngeal structures are but one of several battlefields in the system, and that nature requires reinforcements at all points. Hence while the larynx has not been neglected, more attention has been paid to diet, hygiene, and the maintenance of the general vitality.

Malignant Disease of the Larynx.—The principal lesson of recent years in respect to malignant disease of the larynx is the necessity of an early diagnosis and of energetic local intervention. Semon's contention holds good "that it has been shown conclusively that in a good many of those cases in which the disease begins in the interior of the larynx, more particularly on the vocal cords, it can be lastingly cured by so simple and comparatively non-dangerous operation as thyrotomy with removal of the affected area and a zone of healthy tissue around it, provided only that the diagnosis be made sufficiently early for the

affection to be still limited and circumscribed in character." From which statement is derived the obvious corollary that "obstinate hoarseness in a middle-aged person peremptorily demands a laryngoscopic examination." In a paper by J. N. Mackenzie, entitled "A Plea for Early Diagnosis Naked-Eye and Removal of the Entire Organ with the Neighboring Area of Possible Lymphatic Infection in Cancer" (Transactions of the American Laryngological Association, 1900, p. 56), the author states that there are three methods of diagnosis which in the relative order of their practical usefulness and importance are direct inspection supplemented by clinical phenomena, thyrotomy, and the microscope. He decries the prevalent plan of removing a portion of the growth for examination, claiming that (1) there is danger of autoinoculation at the site of incision and of metastasis elsewhere, (2) that there is danger of stimulation of the local growth of the neoplasm, and (3) that the method is often inconclusive, misleading, and sometimes practically impossible.

This misleading tendency is often occasioned by the fact that the portion removed is merely a scale or chip from the surface and not characteristic of the growth throughout its whole extent. Neoplasms show great differences often between their superficial and deep structure.

Nothing new has been brought forward as to symptomatology or treatment, though the technical features of operative work have been greatly improved. Special attention is now given to post-operative nursing, and the general statistics of the operation are gradually improving. For accurate information upon this latter and most important question the reader is referred to the paper of D. Bryson Delavan (Transactions of the American Laryngological Association, 1900).

There can be no doubt that the operation of splitting the thyroid cartilage with partial removal of the larynx is gaining ground over complete laryngectomy. The terrible mutilation occasioned by the latter, even if the patient survives the operation, must appeal to the surgeon as well as to his patient. It is true that some of these cases learn to speak in a whisper and are not subjected to the annoyance of an artificial larynx. Several instances of conspicuous success in this direction are now on record, but they form a distinct minority. Endolaryngeal methods are applicable to but few of the whole number of cases, although B. Fränkel reported in 1897 some brilliant results by this method. An apt commentary on his statistics is that of J. Wright, who says that "after a careful consideration of Fränkel's paper and a retrospect of his own experience with the disease, the average laryngologist cannot but regard the results attained by Fränkel as an indication of that operator's great manipulative dexterity and of his skill in correctly estimating the extent of involvement of tissue

rather than as a mark which it is wise for every operator to attempt to attain."

The obvious lesson from all this is most carefully to examine every patient in middle life who is persistently hoarse, and if we find in addition an infiltration of the larynx or its adnexa, one of three conditions is probably present: tubercle, syphilis, or malignant disease. The two former must be eliminated by collateral evidence and the general clinical history; this systematic procedure will in the vast majority of cases, when supplemented with the test of the iodide, enable an accurate diagnosis to be made.

Laryngeal Neuroses.—The prescribed limits of this article forbid a discussion of this most interesting and important question. While much clinical research has been carried on during the last five years, it cannot be said that any especially noteworthy discoveries have been made within this period. Attention may be directed to a fair exposition of the present status of the subject by Jonathan Wright in the *Laryngoscope* for June, 1902.

DISEASES OF
THE TRACHEA AND BRONCHI.

BY

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AND

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WITHIN recent years there has been a considerable addition to our knowledge regarding the etiology of inflammatory affections of the trachea and bronchi, bacterial infection being now generally regarded as the most important and most frequent exciting cause of these diseases.

In studying the bacteriology of these tracheal and bronchial diseases, it is evidently a point of great importance to determine whether the normal trachea, bronchi, and lungs contain bacteria. We shall first, therefore, treat of the bacteriology of the normal trachea and bronchi, and of the modes whereby infection of these segments of the respiratory tract is induced, and thereafter consider the various bacteria which may be the exciting cause of inflammation.

The Bacteriology of the Normal Trachea and Bronchi.

Until recently there were two conflicting views on this subject. The opinion entertained by some was that the healthy trachea, bronchi, and pulmonary alveoli always contained microorganisms, and often, if not invariably, contained pathogenic bacteria. But the methods of examination have not infrequently been faulty, the bronchi being examined a considerable period of time after death, for example, or no account being taken of the fact that during expectoration the tracheal and bronchial secretions will become contaminated by the bacteria of the mouth. Pansini's [1] observations on the mucus expectorated by six individuals, whose respiratory tract he regarded as healthy, are, for instance, of but little if any value. Hoffmann [2] stated that streptococcus pyogenes, staphylococcus pyogenes aureus, pneumococci, etc., existed as harmless saprophytes within the bronchi of

healthy individuals, but he does not substantiate his statement by any independent research. Dürck's [8] investigations led him to conclude that the lungs often if not invariably contained bacteria. Béco [9] found bacteria in the normal lungs of man, but stated that the healthy lungs of animals usually contain no microorganisms. Boni [6] almost always found the lungs of guinea-pigs to be germ-free, yet said they might contain pathogenic bacteria. The lungs of recently killed swine, he stated, usually contained bacteria, such as diplococcus pneumoniæ, streptococcus pyogenes, pneumobacillus of Friedländer, staphylococcus pyogenes aureus, and non-pathogenic bacteria.

The majority of investigators, however, have maintained that the lower respiratory passages contain no bacteria. Hildebrandt [6] and Baumgarten [7] determined that the lower respiratory passages and lungs of healthy rabbits are absolutely devoid of microorganisms, but Baumgarten [6] elsewhere says that bacteria are often carried down into the alveoli and thence into the bronchial glands. Babes [6] found, in persons who had died in consequence of some accident but had previously been healthy, that the lower air passages contained no bacteria, and likewise in animals when the smaller bronchi were examined immediately after the animal had been killed. Thomson and Hewlett [10] noted that tracheal mucus from recently killed animals was always sterile. Neisser,[11] examining the lungs of twenty-four small animals, found them completely sterile in twenty-one cases. Klipstein [12] considered that the normal lungs, bronchi, and trachea contained no microorganisms. Müller,[13] in a great majority of his cases, detected no bacteria in the trachea, bronchi, and lungs of small animals. Göbell's [14] investigations on rabbits showed that the normal lungs usually contain no bacteria, although they may occasionally enter through the bronchi. Barthel [15] found that the respiratory tract of healthy rabbits and the lungs of man contained no microorganisms, while the larger and medium-sized bronchi of man almost always contained pathogenic bacteria. Jundell [16] examined the trachea of the human subject during life, and stated that the healthy respiratory tract below the level of the glottis either contains no bacteria or contains a scanty number—chiefly a diplococcus (probably the micrococcus catarrhalis) and a streptococcus—the existence of which is merely transient. Nenninger's [17] investigations showed that the trachea, bronchi, and lungs of sheep, pigs, and rabbits contained but a scanty number of non-pathogenic bacteria or none whatever.

Although from bacteriological examination of the trachea, bronchi, and lungs there is therefore good reason to believe that these portions of the normal respiratory tract contain no bacteria, it may reasonably enough be supposed that the trachea, bronchi, and lungs sometimes contain bacteria—first, because the atmospheric air practi-

cally always contains microorganisms; and secondly, because of the intimate relationship of the larynx to the pharynx. The bacteria of the atmospheric air are for the most part either adherent to fine dust particles or are contained within minute fluid droplets. Flügge [18] and his assistants proved that such minute droplets are liberated from the oral or nasal secretions on sneezing, coughing, and speaking, and these facts have since been confirmed by other investigators (v. Weismayer,[19] Moeller,[20] etc.). The length of time such droplets remain suspended in the air is dependent upon their size, but droplets containing bacilli have been found in the air even one hour after having been liberated from an individual by the act of coughing; and further, a current of air, the velocity of which is less than 0.1 mm. per second, is sufficient to set the finest of these droplets in motion. Nenninger [17] has demonstrated that the current of inspired air will transport bacteria, whether they be in the form of dust or be contained within fluid droplets, into the finest ramifications of the bronchial tubes; and he has shown that, from the fluid secretions of the mouth or pharynx, the current of inspired air is capable of detaching such droplets and of carrying them into the smallest bronchi. Moreover, as the mouth and pharynx always contain various bacteria, it is evident that some of these may be carried into the bronchi with each inspiratory act, and the normal trachea and bronchi cannot therefore be regarded as invariably germ-free.

There are, however, several reasons why bacteriological examination of the normal trachea and bronchi usually shows them to contain no microorganisms. The greater number of the bacteria contained in the inspired air impinge on the mucous membrane of the nasal cavities and are destroyed by the natural bactericidal power of this mucous membrane (Thomson and Hewlett [10]) or by the adenoid tissue of the pharynx (Hildebrandt,[6] Buttersack,[21] Müller,[13] Barlow [22]). But bacteria, carried through the upper respiratory passages and reaching the normal trachea or bronchi, do not then find conditions adapted for their existence and reproduction, for they are either rapidly destroyed, as was demonstrated by the experiments of Lähr,[23] Grammatschikoff,[24] Nebelthau,[25] and Béco,[26] or are carried away by the lymphatics to the bronchial glands. If, however, the tracheal or bronchial mucous membrane be the seat of a local predisposition to disease, or if the vital activity and innate resisting power of the mucous membrane be lowered by predisposing factors—cold or irritant vapors, for example—pathogenic bacteria, whether they be derived from the nasal, oral, or pharyngeal secretions of the individual himself, or from another individual, entering the trachea or bronchi, will find conditions favorable for their growth and development, and will then cause infection. Yet the number of bacteria which enter the

trachea or bronchi is probably a factor of no little importance, and the frequency of bronchitis in children who are habitual mouth-breathers or in persons after tracheotomy has been performed, although perhaps partly due to the fact that the air entering the trachea is insufficiently warmed, is doubtless mainly due to the fact that in such individuals the bacteria of the inspired air have not been arrested by the nasal mucous membrane.

Bacteria Associated with Inflammations of the Trachea and Bronchi.

The causal bacteria of an acute tracheitis or bronchitis are readily detected on examination of the sputum or of the secretion in the tubes post mortem. If the sputum is to be examined, the patient must be directed to cleanse the mouth and to make use of an antiseptic gargle and mouth wash before expectorating; the expectoration must be obtained in a sterile dish, and a portion of the sputum before being examined should be repeatedly washed in sterilized water or saline solution. If these precautions are not taken, bacteriological examination of sputum is rendered almost valueless, owing to the presence of various bacteria derived from the mouth. Thus most of the bacteria found in bronchitic sputum by Babes[27] and Pansini[1] and the bacillus obtained by Grün[28] were almost certainly accidental contaminations from the mouth.

If the secretion is examined post mortem, care must be taken to distinguish between the true causal bacteria and microorganisms—saprophytic bacteria such as are normal inhabitants of the mouth, or bacterium coli commune, for example—which have entered the respiratory tract either during the last moments of life or post mortem.

That there is no specific microorganism causing acute catarrhal inflammation of the trachea or bronchi is shown by a review of the literature.

Troup,[29] in 1886, had described various cocci in bronchitic sputa, but the first researches of importance were those of von Besser,[30] who in eight cases of bronchial catarrh examined the mucus from the main bronchus and found diplococcus pneumoniæ thrice, a streptococcus twice, staphylococcus pyogenes aureus thrice, Friedländer's bacillus once in pure culture, another bacillus, and other cocci. Duflocq and Ménétrier[31] recorded six cases of pulmonary tuberculosis in which there was secondary capillary bronchitis, and in the sputum and in the bronchitic secretion post mortem they found mainly pneumococci in association with staphylococci, less frequently with streptococci or Friedländer's bacillus. Kruse, Pansini, and Pasquale[32] examined thirty influenzal cases and record more especially the detection of a

member of the streptococcus group, although they also noted the presence of diplococci, sarcinæ, and bacilli. A streptococcus was found by Bouchard[33] in bronchial mucus, while in five cases Claisse[34] obtained the streptococcus pyogenes either in pure culture or in association with staphylococci or pneumococci. In eleven cases Queyrat[35] found cocci resembling streptococci, and in five acute cases Dessy[36] isolated a coccus which in some respects resembled a streptococcus and in others the diplococcus pneumoniæ. Babes and Beldimann[37] consider the staphylococcus pyogenes aureus, streptococcus pyogenes, pneumococcus, and mucogenetic bacteria, such as proteus and Friedländer's bacillus, to be the most important causal organisms.

Further, Hoffmann[38] considers streptococci or other cocci to be the most frequent causes of ordinary simple bronchitis. Carrière[39] found the micrococcus tetragenus in one case of severe bronchitis in which empyema was a secondary complication. Barthel,[18] having examined twenty-one cases, regarded the diplococcus pneumoniæ as the most important bacterium causing bronchitis, this coccus being detected in twelve cases, in each of which there were marked changes in the bronchial mucous membrane; streptococci were regarded by Barthel as of less etiological importance, and staphylococcus pyogenes he considered the least important of these three bacteria.

The expectoration from thirty cases of acute bronchitis was examined by Jundell.[40] He found almost no bacteria in nineteen cases, numerous streptococci and also pneumococci in two cases, bacillus catarrhalis (which resembles the influenza bacillus) in three cases, the true influenza bacillus in one case, and bacillus catarrhalis and diplococci resembling the diplococcus intracellularis meningitidis of Weichselbaum in two cases.

One of us[41] examined bronchitic secretion post mortem in twenty-seven cases of acute bronchitis in children, and in twenty two cases in which there were both bronchitis and pneumonia. The investigation of these forty-nine cases showed that in practically every case of acute bronchitis there were *numerous* pathogenic bacteria in the bronchitic secretion. In but few cases, however, was any bacterium present in pure culture, and catarrhal bronchitis must consequently be regarded as the result more frequently of mixed infection than of infection by any one microorganism alone. We found that the two most important causal bacteria were (*a*) diplococcus pneumoniæ and (*b*) streptococci. Diplococcus pneumoniæ was isolated in twenty-three cases; in two instances the bronchitis was caused by this diplococcus alone; in the remaining cases these diplococci were associated with streptococci, influenza bacilli, staphylococci, diphtheria bacilli, or bacillus pyocyaneus. A member of the streptococcus group appeared to be the sole causal bacterium in eight cases, while streptococci were

present together with other pathogenic bacteria in nineteen cases in which the bronchitis was probably the result of mixed infection. The influenza bacillus was cultivated in seventeen instances, all of which were probably sporadic cases of influenza. The bacillus was most frequently associated with diplococcus pneumoniæ or with streptococci.

The micrococcus catarrhalis was first observed in bronchitic sputum by R. Pfeiffer. Frosch and Kolle [42] considered this Gram-negative intracellular diplococcus to be identical with the cocci previously detected by Seifert,[43] but Ghon believes that Seifert's cocci were probably members of the streptococcus group. Ghon, H. Pfeiffer, and Sederl [44] have again drawn attention to the micrococcus catarrhalis as an exciting cause of acute bronchitis as well as of bronchopneumonia. In a series of one hundred and thirty-two cases, this coccus was isolated no less than eighty-one times. It was found in pure culture in one case of diffuse purulent bronchitis; in five cases the same coccus was the cause of bronchitis and pneumonia, while in the remaining cases there was either a mixed infection or the coccus was present so scantily as compared with other bacteria that it had probably no causal relationship to the disease.

Acute catarrhal inflammation of the trachea and bronchi, except when caused by the influenza bacillus, is less frequently induced by bacilli than by cocci. Friedländer's bacillus, for instance, appears to be as infrequent a cause of bronchitis as of pneumonia. Von Besser, as already mentioned, found this bacillus once in pure culture. The same bacillus in association with diplococcus pneumoniæ was recorded in one case by Jaccoud,[45] and in association with scanty cocci by Mandry.[46] Silvestrini [47] and Wright and Mallory [48] have each recorded one case in which Friedländer's bacillus was apparently the exciting cause of bronchitis; while in our series of forty-nine cases, bacilli belonging to the group of capsuled bacilli were isolated only three times—once in pure culture, but for bacilli of the coli group, and twice in association with streptococci or other bacteria.

When diphtheria bacilli have been isolated from the bronchi, a local diphtheritic membrane has as a rule been present. In six cases of our series, however, there was no such diphtheritic membrane in the bronchi, and yet in each instance the diphtheria bacillus, together with other bacteria, had probably caused the bronchitis.

In epidemic influenza the specific bacillus is frequently the exciting cause of bronchitis and tracheitis. Yet, as we have already stated, bronchitis is probably not infrequently due to the influenza bacillus apart from epidemic influenza. Lindenthal,[49] for example, has reported eight cases of sporadic influenza, with bronchitis and pneumonia, in which the influenza bacillus and diplococcus pneumoniæ were

found in the bronchitic secretion; while Kretz [60] cultivated the same bacillus from the sputum of thirty-five cases, in none of which were there typical signs of influenza; and Washbourn [61] has recorded a case in which the influenza bacillus was present, although the clinical aspect of the case was that of a simple catarrh. It must, however, be noted that in cases of acute bronchitis Elmassian [62] found a bacillus which was very similar to the true influenza bacillus in all respects, except that it could be cultivated on media containing serum or ascitic fluid, and that he does not attribute to this bacillus any etiological importance in the causation of bronchial infection.

Again, the bronchitis associated with whooping-cough is doubtless due to the microorganism causing this disease; but the nature of this virus being still undetermined, it is only necessary to make mention of the bacteria described by Czaplewski and Hensel,[63] Vincenzi,[64] Spengler,[65] Jochmann and Krause,[66] and the amœba which Behla [67] claims to have observed in the mucus.

The conclusions, then, which may be drawn from these numerous investigations are that bacteria are the exciting cause of acute catarrhal inflammation of the trachea and bronchi, that the process is usually the result of mixed infection, and that it is more often caused by the diplococcus pneumoniæ or by streptococci than by any other bacterium.

The bacteriological aspect of *chronic catarrhal inflammation of the trachea and bronchi* has not been the subject of much research. Cassaët,[68] indeed, found streptococci in the sputum of four cases of chronic bronchitis, and Hayo Bruns [69] states that there were pneumococci and also other microorganisms in the sputum of a man suffering from chronic bronchitis with bronchorrhœa. That it is difficult in chronic bronchitis to draw definite conclusions from bacteriological examination of sputum or of secretion post mortem is apparent when we remember that in such cases the mucous membrane of the trachea and bronchi presents conditions not unfavorable for the existence and reproduction of the various pathogenic and non-pathogenic bacteria which may from time to time enter the bronchi, and that the growth of the primary causal microorganisms may be inhibited by the development of various secondary bacteria. The flora of the trachea and bronchi in these cases is consequently very varied; mixed infection is common, and, further, saprophytic bacteria, such as pseudo-diphtheria bacilli, sarcinæ, air cocci, etc., are not infrequently present.

Putrid Bronchitis.—The bacteria associated with this variety of bronchitis have been as yet imperfectly investigated. Lumniczer [70] from one case isolated several cocci and a bacillus which Kruse [71] terms bacillus bronchitidis putridæ. Alfieri [72] and Bernabei [73] described a

motile bacillus which the latter designated as B. putridus splendens and regarded as the cause of primary fetid bronchitis. The bacterium coli commune is, however, apparently the causal microorganism in some instances, for Hitzig [64] in one case isolated two forms of bacilli belonging to the coli group, and Noica [65] also records B. coli in association with staphylococci in fetid bronchitis.

Fibrinous Bronchitis.—The etiology of this comparatively uncommon variety of bronchitis is still a matter of much dubiety. Sokolowski [66] in four cases found that staphylococci were the chief bacteria present, and in one instance staphylococcus pyogenes albus was found in pure culture by Nachod.[67] Lépine [68] considers the pneumococcus to be one of the more important bacteria causing pseudomembranous bronchitis, and, lastly, Ott [69] found Fraenkel's diplococci and staphylococci in the bronchial casts obtained from a chronic case of this form of bronchitis.

In the present state of our knowledge, therefore, we must admit that the bacteriology of fibrinous bronchitis is as yet very incomplete; still it is not infrequently supposed that the exciting cause is in each instance some pathogenic microorganism. In the case of acute fibrinous bronchitis this supposition is probably correct, but in the chronic cases there is no doubt some other concomitant causal factor.

There is still no unanimity of opinion regarding the constitution of the casts expectorated from the bronchi. The greater number of writers have stated that these casts consisted mainly of fibrin, but of late several observers have shown that the chief constituent of the casts may be mucin and not fibrin. Habel,[70] for instance, examined bronchial casts from three cases. He found that the casts did not stain by Weigert's method, and were consequently not composed of fibrin, while he further determined that the casts gave the characteristic chemical reactions of mucin and that they were acid in reaction. He therefore assumed that the mucus secreted into the bronchial lumen had become coagulated owing to the reaction of the bronchial secretion having been rendered acid by bacteria. We may further note that this theory propounded by Habel receives support from the fact already recorded that the ordinary staphylococci have been found in similar cases and that these cocci render acid the reaction of the media in which they are cultivated. Of other observers who determined that the casts are mainly mucinous in nature, we may mention Beschorner,[71] while of recent writers who found that the bronchial casts were essentially fibrinous the names of Strauss [72] and Schittenhelm [73] may be noted.

A point of further importance is that in cases of bronchial asthma fibrinous casts have been detected in the sputum, and as Charcot-Leyden crystals and eosinophile cells may be present in the sputum in

cases of fibrinous bronchitis, it has been maintained by some authors that there is an intimate relationship between these two diseases.

Bronchiectasis.—There have been but few new facts of importance regarding this disease recorded in the literature since 1896. To two points, however, reference must be made. The first of these is related to the bacteriological examination of the sputum as a means of diagnosing bronchiectasis from pulmonary phthisis. Until recently it was supposed that an individual was affected with pulmonary phthisis if he presented signs of pulmonary disease and was expectorating bacilli which, after having been stained with warm carbol-fuchsin, resisted decolorization with mineral acids, and that consequently the mere detection in films of bacilli which resisted such decolorization sufficed to differentiate pulmonary tuberculosis from bronchiectasis or other condition, the symptoms of which resembled those of phthisis. That a diagnosis based on the detection of such bacilli in films made from the expectoration may be incorrect is illustrated by the case recorded by Pappenheim,[74] in which acid-proof bacilli were found and a diagnosis of tuberculosis was accordingly made, the case being, however, not one of tuberculosis but of chronic bronchitis with bronchiectasis and a small area of pulmonary gangrene. The presence in sputum of acid-proof bacilli other than tubercle bacilli has, moreover, been recorded by A. Fränkel,[75] L. Rabinowitsch,[76] Folli,[86] Lubarsch,[87] Lichtenstein,[88] and others. As it is not always possible to differentiate tubercle bacilli from other acid-proof bacilli by morphological and staining characters alone, an attempt should be made in every doubtful case to cultivate the bacilli, and guinea-pigs or other susceptible animals should be inoculated.

Rist[77] has recently drawn attention to the occurrence of putrid suppuration as a secondary complication of bronchiectasis. In one case the most abundant bacterium in the pus of the secondary empyema was an anaerobic, capsuled, Gram-positive diplococcus, which was morphologically very similar to the diplococcus pneumoniæ; while in a second case of bronchiectasis the same anaerobic bacterium was obtained from metastatic subperiosteal abscesses of the femur.

Another sequela of bronchiectasis, the importance of which has been of late much emphasized and to which it will suffice to make reference, is *osteopulmonary arthropathy*, which, as is well known, is also a secondary phenomenon in cases of chronic bronchitis, chronic phthisis, empyema, and tumor of the lung. In this form of arthropathy the hands are enlarged, the extremities of the fingers are clubbed, the terminal phalanges being large and broad, the nails of large size and markedly convex. There is also enlargement of the bones of the lower part of the forearms and legs and those of the feet, but the bones of the skull are unaffected. The pathogenesis of the condition is at present a matter of doubt.

Compression of the Trachea.

Apart from compression and stenosis of the trachea produced by the more common lesions—bronchocele, enlarged mediastinal glands, retropharyngeal abscess, malignant disease of the œsophagus, and aortic aneurysm—there has been again within the last few years a considerable amount of work dealing with the subject of tracheal compression and stenosis, more especially in children, induced by hypertrophy of the thymus. This gland is hypertrophied to a greater or lesser degree in the condition termed lymphatism or status lymphaticus, in one form of which, however, the enlargement of the thymus is very pronounced, while the hyperplasia of lymphoid tissue in the pharynx, spleen, intestine, and generally throughout the body is proportionately not so well marked. It is in regard to this latter form of lymphatism that the question arises as to whether tracheal compression and stenosis can be produced by the hypertrophied thymus—a question upon which until recently different writers manifested no unanimity of opinion.

Paltauf [78] and others considered that the fatal termination in these cases was not due to tracheal compression, and Paltauf maintains that associated with general hyperplasia of the lymphoid tissue there is arterial hypoplasia, and that death results from acute cardiac dilatation. Others, such as Purrucker [79] and Seydel, [80] assume that death results from pressure of the thymus on the vagus or recurrent laryngeal nerves, while Dixon [81] and Kohn [82] record cases in which the pressure was apparently exerted on the aorta or large vessels.

There is, however, no doubt that the hypertrophied thymus may produce fatal compression of the trachea, and although it is recognized that in lymphatism the fatal issue is not usually the result of tracheal stenosis, yet the possibility of such an occurrence is now generally recognized. There are, however, on record but few cases in which the tracheal stenosis has been definitely demonstrated. Of such cases we may note that recorded by Clessin, [83] in which the tracheal stenosis at a point 2 cm. above the bifurcation was so great that the anterior and posterior aspects of the trachea were in contact with each other; and again, a case of Lange's, [84] in which there was marked anteroposterior flattening of the trachea; and, lastly, the seven cases recorded by E. Flügge. [85] There are, moreover, on record a few cases which were saved, or in which the condition of the patient was materially improved, by the thymus being removed from the mediastinum and fixed to the tissues of the neck.

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DISEASES OF THE LUNGS.

(EXCLUDING CROUPOUS PNEUMONIA AND TUBERCULOSIS.)

BY

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Post-Operative Lung Complications.

THE importance of lung complications after operations, is a subject not sufficiently treated of in our medical and surgical works. When we consider that there is a mortality in some countries of from five to ten per cent. from lung complications following major operations, one must pause to reflect. This is a greater mortality than we have in appendicitis or after hysterectomy. And we furthermore believe this post-operative mortality from pulmonary complications can be reduced to less than one per cent.

In 1898 Gottstein reported in the *Archiv für klinische Chirurgie* from Breslau 27 cases of lung complications under local anæsthesia following 114 laparotomies, or about 15 per cent. The same writer calls attention to 119 cœliotomies under general anæsthesia with 7 cases of lung complications, or 6 per cent.

Mikulicz, in the German Surgical Congress, 1901, cites over 1,000 cases of major operations under general anæsthesia, with 7.5 per cent. of pneumonia and 3.4 per cent. of mortality; and 273 cœliotomies under local anæsthesia, with 12.8 per cent. of pneumonia, with a mortality of 4.8 per cent.

Etiology.—In an excellent article upon the subject, in the *Deutsche Zeitschrift für Chirurgie*, 1901, Gerulanos summarizes the causes of post-operative lung affections as follows:

1. The direct irritating action of the anæsthetic on the respiratory mucous membrane, with hypersecretion. This is more marked in ether narcosis.

2. The toxic effect of the anæsthetic on the blood-vessels, producing dilatation of the vessels, hyperæmia, and œdema of the lungs, with the usual secondary effect on the heart. This is present after both

chloroform and ether, but more marked in the latter. This condition favors hypostatic pneumonia and lowers the resistance of the lung tissue to infection.

3. The inspiration of infected material from the secretions of the mouth and pharynx, or of vomitus.

4. Infected or non-infected emboli from thrombosed vessels (usually veins) at the site or in the neighborhood of the operation.

5. Chilling, fright, and shock from the operation, with or without hemorrhage, all lower the resistance of the patient and act as indirect factors in the production of the pneumonia. (Prolonged general narcosis, long exposure of the chest or peritoneal cavity, reduce the temperature.)

6. A general weakness of the patient lowers the resistance and acts as a very important indirect factor.

7. The restriction of respiration, and especially expectoration, by the pain of the abdominal wound or the tight bandage.

The direct irritating action of the anæsthetic on the mucous membrane of the respiratory tract is considered from experimental investigation not to be a very important factor.

Lindemann and Hölscher say that hypersecretion is a more important factor, in that it increases the possibility of inspiration of infected material.

The toxic effect on the blood-vessels of the anæsthetic circulating in the blood is a very important factor. Lindemann, in his experiments on animals with ether narcosis, demonstrated this vessel dilatation with hyperæmia and œdema of the lungs and a secondary effect on the heart. This lung œdema is present during and for a number of hours after the narcosis, and Lindemann concludes that it lowers the resistance and increases the possibility of aspiration pneumonia, and may of itself in certain individuals produce hypostatic pneumonia. Hölscher practically confirms Lindemann's experiments.

There is no question about the possibility of inspiration of infected material. Numerous experiments on animals have demonstrated this, and autopsy findings of material in the trachea and bronchi confirm it (Lindemann and Hölscher). The danger is increased when there are suppurative inflammations or wounds of the mouth and pharynx. It has been demonstrated that prolonged and proper disinfection of these cavities decreases the danger somewhat. Larger particles of infected material, especially vomitus, in ileus, etc., are more dangerous. It is to be remembered that the inspiration of infected material during vomiting may take place without general narcosis.

Embolic pneumonia is independent of the general narcosis, and is due entirely to the nature of the operation and the disease. This has been carefully studied by Gussenbauer and Lesshaft, Klemm and

Bayer, and Fischer and Levy. In strangulated hernia and other forms of ileus, whether the gut is gangrenous or not, the mesenteric vessels, chiefly the veins, are frequently thrombosed beyond the seat of the constriction, and when the constriction is relieved and the gut reduced emboli may form and reach the lung. The emboli of themselves may be infected, and, if so, produce at once in the lungs an area of pneumonia; or, if not infected, the infarct is an area of lower resistance and may become secondarily infected from bacteria already in the bronchi in cases of chronic bronchitis, from infected particles, or from the blood. These emboli may lodge after any operation before or at the time of which there was thrombosis of the vessels. It is not an infrequent occurrence in gynecological operations to find various infected and non-infected conditions of the pelvic organs. Embolism has been noted after Alexander's operation and operations for inguinal hernia from thrombosis of the spermatic veins. In operations for various infections of the extremities, septic emboli may be loosened and reach the lungs. It has been noted after extensive head operations by Kocher and others. On the whole, it is much more common after laparotomies. It is not uncommonly noted secondary to phlebitis of the lower extremity, which condition, we know, is more common after laparotomy. The more one studies the records of post-operative lung complications, the more convinced he becomes that embolic pneumonia is the chief cause and explains many of the cases recorded after local anæsthesia.

Chilling, fright, shock, prolonged narcosis, and exposure of the chest and peritoneal cavity are commented upon by all authorities as indirect causes which should be avoided when possible. It is unnecessary to comment upon the increased danger of lung complications in greatly debilitated patients.

Czerny, quoted by Nauwerk, and others draw attention to the possibility that the pain from the abdominal wound or the restriction by the tight bandage on the abdomen and chest greatly inhibits respiration. They find that these patients will not expectorate, and think these factors increase the danger of lung complications, especially in debilitated patients and those having chronic bronchitis. The absolutely quiet and prolonged dorsal position of the patient, especially when in a debilitated condition, greatly favors hypostatic congestion and its results.

All these causes acting in various combinations may produce bronchitis, bronchopneumonia, lobular pneumonia, acute œdema of the lungs, hemorrhagic infarcts, gangrene, or abscess. Gangrene and abscess fortunately are most rare, and are due to the inspiration of large infected particles or infected emboli, which depend little, if at all, upon the general narcosis.

The general narcotic acts as a slight irritant, producing hypersecretion, and on the blood-vessels, causing hyperæmia and œdema, by lowering the temperature, and by increasing the possibilities of inspiration on account of the muscular relaxation.

Prophylaxis.—Over some of the causes of post-operative lung complication we have some control, over others none.

Schultz, from a careful study of four hundred and sixty cases of ether narcoses and one hundred and ninety-three chloroform narcoses, all for grave operations, finds that lung complications are less frequent after ether narcosis, and recommends it in these prolonged operations on account of its good effect upon the heart and circulation, the absence of fatty degeneration of the internal organs, and the slight injurious influence on the kidney. This question, however, does not seem to be settled.

If the operation is of short duration and can be done under local anæsthesia, this should be attempted, especially if the patient is suffering with some lung lesion or is greatly depressed from some grave infection or disease, as, for example, strangulated hernia, typhoid perforation, empyema. Local anæsthesia is advisable also in operations like gastrostomy and colostomy for advanced carcinoma.

When a general anæsthetic is necessary, it should be given with the greatest care; if possible, the narcosis should be an interrupted one, and the least possible amount of anæsthetic should be given. This partial and interrupted narcosis is the most important, and is commented upon by a number of authorities; with it it is even possible to do extensive abdominal operations, especially if the incision is a large one. Both chloroform and ether can be used in this way. It is sometimes better to begin the narcosis with chloroform, as it is less apt to produce vomiting, and change later to ether, which should be continued if the patient does well under this anæsthetic. When the patient does not do well, but secretion of mucus, cyanosis, or vomiting occurs, it is on the whole better to return to chloroform, unless there is a distinct contraindication on account of the condition of the heart or the pulse. If the patient is suffering with chronic bronchitis or any other acute or chronic lesion of the lung, chloroform becomes the anæsthetic of choice. Many of these patients, however, take the ether well, with little or no hypersecretion of mucus. If such is the fortunate result the ether should be continued throughout the operation. Ether when well taken seems to be the anæsthetic of choice in long and grave operative procedures, even laparotomies, in debilitated individuals.

There is little to do to prevent the toxic effect of the anæsthetic on the blood-vessels, except to diminish the amount of the anæsthetic and the duration of the narcosis as much as possible. It is in these cases

that the skill of the anæsthetist and the rapid operator add so much to the probabilities of a successful result.

Much can be done to prevent the inspiration of infected material from the mouth or stomach. Previous to operation the mouth and pharynx should be carefully disinfected. During the operation no material should be allowed to accumulate in the pharynx. This is best accomplished by the lower position of the head, known for a great number of years by surgeons as Roser's position.

Personally I am of the opinion that the elevated position of the patient—Trendelenburg's position, and, in addition, when excessive mucus is present or vomiting occurs, allowing the occiput to drop over the edge of the table, and holding the jaws forward—should be a routine procedure in all cases in which, on account of the nature of the operation and disease or of the condition of the patient, lung complications are apprehended. I was brought to this conclusion by a comparative study of about five hundred cases of inguinal hernia, in which the operation was usually done in the horizontal position, with an equal number of operations for hemorrhoids and fistula in ano, in which the operation was performed in the elevated position just described. In the latter, lung complications were practically absent, with no mortality; in the former, pneumonia was present in about two per cent. of the cases of non-strangulated and eight per cent. of strangulated hernia. We know very little about the cause of thrombosis and emboli, and as yet we are ignorant as to its prevention.

The chilling of the patient can be prevented, but eternal vigilance on the part of the surgeon and the nurse is necessary. Unfortunately the proper precautions are frequently neglected. The fright and nervousness of the patient can be greatly lessened by thoughtful and judicious care. Shock from hemorrhage in the majority of instances is under the control of the surgeon. It is safer to operate more slowly with a minimum loss of blood, than rapidly with a maximum loss of blood. Prolonged narcosis cannot always be avoided; its dangers can be lessened greatly by the interrupted method. Exposure of the chest and peritoneal cavity can usually be avoided or reduced to a minimum by increasing the temperature of the operating-room and by the proper protection of the viscera by warm towels, gauze, or sponges. The preparation of greatly debilitated patients for operation is a serious one. If the operation is one of emergency, little can be done except subcutaneous infusion before, during, or after the operation. If it is not, something may be accomplished by very careful diet, and in stomach cases by rectal feeding.

In this group of cases under discussion surgeons recommend that the abdominal and chest bands should be loose; the patient after the operation should be encouraged to inspire deeply and expectorate if

possible. In very weak patients it will be necessary for the nurse to aid them to keep the mouth and pharynx clean, especially when they vomit. Minute doses of morphine decrease the pain from the abdominal wound, and, on the whole, make respiration easier. Abdominal distention should be prevented if possible by proper means, as it undoubtedly inhibits deep and proper respiration.

In debilitated patients and those whose circulation is feeble, the danger of hypostatic congestion and pneumonia is greatly increased. These patients should have their position in bed frequently changed, first on one side and then on the other, and a partially elevated position of the chest and head. The prolonged flat dorsal position should be avoided.

In a certain group of cases, especially all forms of intestinal obstruction and in cases in which on account of the emergency of the operation it has been impossible to have an empty stomach, the stomach should be carefully washed out previous to operation. This can frequently be done after the patient is in general narcosis.

For extensive operations on the stomach and intestine in which it is possible to have a number of days for preparation, Harvey Cushing's advice should be followed. Cushing recommends the feeding for a number of days with sterilized liquid food and water. His experiments on animals and clinical observations have demonstrated that this method diminished greatly the number and virulence of the bacteria in the intestinal canal, and, therefore, the possibility of infection following operation.

In many thousands of cases of anæsthesia for major and minor operations, two-thirds of which were chloroform narcosis, a few cocaine (spinal) analgesia and local anæsthesia, and the rest ether narcosis, we have not had a death from lung complications in St. Winifred's Hospital, San Francisco. This I attribute to our strict antiseptic precautions in the matter of antiseptic gargles for patients, aseptic (sterile) air in the warm operating-rooms, and warm rooms for patients, as well as the greatest care in the administration of the anæsthetic. Prior to a cœliotomy the patient's alimentary canal is thoroughly evacuated, first with blue mass gr. x., followed by several ounces of saturated solution of sulphate of magnesium. Liquid pre-digested food is used for forty-eight hours prior to an operation, and the following is given:

℞ Salolis ..... gr. i.
Bismuthi subnitratis ..... gr. iiss.
Carbonis animalis ..... gr. v.

M. et flat chartula No. i. S.: One such powder every three hours for forty-eight hours before an operation.

This with an antiseptic nasal spray and mouth wash renders the whole alimentary canal aseptic and free from flatus.

Blood-vessels are clamped the instant they are cut. This lessens the liability to air absorption and embolic infection. Fright is seldom observed, and chilling we prevent by having warm operating-rooms, 80° to 90° F. in cœliotomies, and warm rubber covering for chest and abdomen.

The restriction of respiration is measurably overcome by rubber adhesive straps which reach only *two-thirds* around the body. Operations should be performed as expeditiously as possible and with a minimum loss of blood. The after-treatment in abdominal section is very important to prevent lung complications. Always have the patient in a warm room. Use rectal alimentation and stimulation. Change the patient every few hours from one side to the other. The dorsal decubitus is necessary in but very few cases.

The most important after-treatment consists in free purgation the second day after an operation. This will remove the possibility of tympanites, peritonitis, and autointoxication, and give the patient a much better chance to fill the lungs with air and to cough and expectorate when necessary.

Hyperæmia of the Lungs.

This condition, which is the forerunner of so many lung diseases, requires careful consideration. Prompt and energetic action will prevent graver sequelæ and often abort serious complications.

Treatment.—In acute congestion of the lungs prompt action is of the utmost importance. At St. Winifred's Hospital, San Francisco, we place the patient as early as possible in the hot dry-air apparatus, running the temperature up to 300° or 350° F. for fifteen to twenty minutes, giving hot drinks internally in the way of lemonade, hot whiskey punch, hot broth, etc. The patient is then placed in bed in warmed blankets, and in acute sthenic cases one-tenth of a grain of pilocarpine is given hypodermically. This insures profuse perspiration for two or three hours, at the end of which time the pulmonary hyperæmia is invariably considerably lessened. In the active or sthenic variety of pulmonary hyperæmia, phlebotomy is practised in selected cases with decided benefit. In cases in which phlebotomy is not advisable, small doses of aconite or of veratrum viride, with or without jaborandi or pilocarpine, have proven very beneficial. The use of a brisk cathartic of calomel and jalap, followed by saturated solution of magnesium sulphate so as to unload the chylopoetic circulation, is a valuable adjunct in the treatment of these acute hyperæmias. Having established free diaphoresis and free catharsis, it is advisable to direct our attention to the kidneys. For this purpose acetate of potassium and squills with sweet spirit of nitre and strophanthus will

be found highly satisfactory. In the rheumatic or gouty diathesis salicylate of lithium and sodium or colchicum is indicated. When the hot dry-air apparatus is not at hand, a hot general bath will be found very beneficial, or hot turpentine stupes to the chest applied every few minutes for an hour or more may be substituted. In this manner acute congestion of the lungs can be invariably relieved, and what would otherwise go on to a severe bronchitis or pneumonia may be prevented. In the chronic, atonic, passive hyperæmia of the lungs, or hypostatic congestion, our remedies must of necessity vary according to each case. As a rule the *cause* of the congestion of the lung should be treated; such, for instance, as valvular disease of the heart. Should there be hydrothorax or ascites, the fluid must be removed from the thoracic or abdominal cavity. In hypostatic congestion of the lungs, which is apt to occur in long-continued fevers, such as typhoid, remittent fevers, etc., and severe surgical operations or broken bones requiring dorsal decubitus for a long period of time, great care must be exercised. The patient's position should be changed every few hours, even if it be only a slight elevation of a few inches on each side at the time. Vigorous stimulating massage of the chest walls will prove beneficial. Daily dry-cupping over various portions of the chest with change of position is found to be useful. The internal administration of strychnine, phosphorus, ferruginous tonics, suprarenal, orchitic, or brain extracts, and arsenic has proven beneficial in the writer's hands; keeping the alimentary canal and the skin and kidneys in as normal a condition as possible is to be desired. Stimulating expectorants, such as senega, turpentine, wood tar, and ammonium carbonate, to relieve the engorgement, also assist materially. Inhalation of hot steam laden with various medicaments has also proven serviceable. Massage of the chest walls and exercise with the arms in suitable cases seem to assist in relieving the engorgement of the lungs. Breathing exercises, whereby deep inhalations and exhalations are taken, have also been beneficial.

Acute Idiopathic Pulmonary Congestion (Moillez's Disease).

This is a pulmonary congestion due to simple exposure to cold and occasionally to injury, the symptoms ensuing in a few hours. It often occurs on one side only. It may be observed in persons of weakly constitution who are induced to take a cold plunge in sea water when the temperature is 35° F. or below. It may occur in a boxing bout when one side of the chest has been more punished than the other. The affection lasts from two to five days, and should not prove fatal if appropriate remedies be used, such as hot applications to the extremities, strychnine, cardiac stimulants, and thorough purgation with

salines. Diaphoretics and diuretics should be given freely. The atmosphere about the patient should be moist and warm, and counter-irritation to the chest walls is advisable.

The continuous inhalation of chloride of ammonium for hours and days is highly extolled as an abortive treatment in acute hyperæmia of the lungs. By placing a common soup plate beside the bed and pouring into it four ounces of strong sulphuric acid, then sprinkling it over with common salt, and placing within this plate a saucer containing two ounces of strong ammonium hydrate, the room will be quickly filled with a dense fume of nascent ammonium chloride. In acute hyperæmia Mendel's solution is advocated as an intratracheal injection. Mendel's solution is composed of: Essence of thyme, essence of eucalyptus, essence of cinnamon, of each 5 gm.; olive oil (sterilized), to make 100 c.c. Of this solution 3 c.c. are injected four times a day.

Pulmonary Puncture—Pulmonary Phlebotomy.—McAllister, of Liverpool, and Blair Bell have successfully treated indolent congestion by exposure with the aspirating needle, and Bell has bled the lung by means of a trocar and cannula (*British Medical Journal*, November, 1900). Simpson speaks of the new treatment of bleeding in some cases of pulmonary congestion, and the late George Harley suggests the name of pulmonary phlebotomy. The puncture is made into that portion of the lung in which there is most congestion, and an ounce or two or more of blood is aspirated with decided benefit.

Pulmonary Hemorrhage—Hæmoptysis.

True pulmonary hemorrhage when slight generally comes from the bronchial mucous membrane, as in bronchitis, congestion, or pneumonia, or from a pulmonary apoplexy. When it is profuse, coming up by the mouthfuls, it is usually caused by the rupture of an eroded blood-vessel in a phthisical cavity or from syphilitic or malignant ulceration or an aneurysm.

Treatment.—The treatment of hæmoptysis must be symptomatic and causal. The blood may come from the nose, for instance, or the throat. It may come from the stomach, or it may have been swallowed from a nasal hemorrhage and appear as hæmatemesis. When the hemorrhage is slight, as we find it in bronchitis, congestion, etc., no special treatment is indicated, excepting keeping the patient quiet and addressing appropriate remedies. When the hemorrhage is severe, active measures must be employed. The patient should occupy the recumbent position so as to quiet the circulation. All his anxiety should be removed and no exertion should be permitted. Excited friends should be removed from the room. The apartment should be kept cool and well ventilated. Ice bags or the Leiter coil may be

applied to the chest and back of the neck. Small pieces of ice may be sucked. One-one-hundredth of a grain hypodermically of atropine has also assisted the writer in checking hemorrhage from phthisical cavities. Chloride of calcium (gr. v.–x.), with an emulsion of turpentine and deodorized tincture of opium, has given satisfaction in severe hæmoptysis. The addition of half an ounce of gelatin daily to the patient's diet is recommended. Hypodermic injections of gelatin solution and calcium chloride may be used. Sulphuric acid lemonade, iced, is also recommended, as are teaspoonful doses of chloride of sodium in iced water. The iron spray and the alum spray have been employed. Suprarenal extract as a spray is also used. Should the hemorrhage come from a ruptured aneurysm and surgical interference is not possible, there is very little that can be done besides keeping the patient quiet and cool and administering hypodermics of morphine, atropine, and hydrastin. In the circumscribed or nodular hemorrhage occurring from the rupture of capillaries in the small pulmonary arterioles—the so-called hemorrhagic infarct or pulmonary apoplexy—the treatment must be directed to the cardiac, renal, or pyæmic diseases inducing the hemorrhage. In the internodular and petechial hemorrhages of the lungs which occur in pyæmia, puerperal fever, purpura, typhus, smallpox, and malignant septic fevers, the treatment must of course be directed to relieving or removing the etiological factors. Ergot and astringents are no longer considered of any use in hemorrhage from the lungs. A more rational method of treatment consists in allaying the cardiac excitement by means of the early hypodermic administration of morphine, to allay the cause and concurrent vascular tension, followed as rapidly as possible by quickly acting purgatives. Hydrastis canadensis in half-drachm to drachm doses, given every three to six hours, has a decidedly beneficial effect in arresting pulmonary hemorrhage. Chloral, gr. v., is of value as a vasodilator; ipecacuanha in emetic doses arrests hæmoptysis. Tincture of hamamelis in drachm doses every two hours has also been used with success. Hepatic extract or suprarenal extract, in doses of one to four drachms by the mouth or by the rectum, has a decidedly beneficial effect. Turpentine, in ten-drop doses every three hours, and oil of erigeron in twenty-minim doses administered on a lump of sugar every hour, has also assisted in arresting pulmonary hemorrhage. Dermatol and stypticin are useful at times. Saline hypodermoclysis, together with the inhalation of oxygen, has been used with beneficial results in severe pulmonary hemorrhage. Gelatin solution injected subcutaneously is of specific value in severe hemorrhages from any part of the body. Thirty per cent. of gelatin in decinormal salt solution, with one grain of carbolic acid for each cubic centimetre of solution—of this use 2 or 3 c.c.

Œdema of the Lungs—Pneumochysis.

Œdema of the lungs may be general or local. It may involve one entire lung or both, or it may attack only limited areas.

The *treatment* must be prompt and energetic. Life may often be saved by the prompt action of the physician in such cases. In the very acute variety and in plethoric patients I do not hesitate to withdraw from eight to sixteen ounces of blood from the arm or to use twenty to forty dry cups over the front and back of the chest walls, followed by a generous cataplasm of half mustard and half flour, keeping it on one hour, after which I use a stimulating turpentine liniment, followed by a large poultice. In œdema of the lungs, the heart, the liver, and the kidneys are usually found to be seriously affected, and our treatment must be directed to these organs accordingly. One of the best heart and lung stimulants I have found is nitrate of strychnine given hypodermically, using one-thirtieth of a grain every fifteen to sixty minutes, according to the urgency of the case, until one-tenth of a grain has been given. This will frequently stimulate the circulation sufficiently to rid the lung of some of its transudation serum. The free administration of oxygen will be found to assist materially during this process and drain the lung tissues. One-fiftieth of a grain of nitroglycerin given hypodermically will relieve peripheral pressure. One-fiftieth of a grain of digitalin given hypodermically with one-one-hundredth of a grain of atropine hypodermically will be of service in stimulating the heart and checking excessive transudation. Active purgation by means of calomel and compound jalap powder should be established as early as possible. Diuretics (diuretin) and diaphoretics (pilocarpine) should be made use of as early as the case warrants. Should the strength of the heart be insufficient to reëstablish the pulmonary circulation, the administration of sixteen to thirty-two ounces of decinormal salt solution under each breast by means of hypodermoclysis will be found exceedingly valuable. The administration of brandy, two to four ounces at once in strong coffee, will assist in stimulating the heart's action and tiding the patient over a critical point. The hypodermic administration of ether will assist the strychnine and digitalin in keeping up the heart's action. Nuclein, spermin, and brain extracts hypodermically are well worth trying. Should the lungs be much engorged in the course of a few hours, squills, buchu, and acetate of sodium or potassium will prove valuable as diuretics. The lungs may be relieved by the use of senega, serpentaria, Hoffman's anodyne, ammonium iodide and carbonate, and other stimulating expectorants. Hot dry air with a large supply of oxygen has proven of great value in severe cases of pulmonary œdema.

In chronic diseases with progressive cardiac weakness very little

can be done for œdema. When congestive œdema is due to exposure or to fatigue in cases of chronic renal disease, a condition known as renal asthma supervenes. In such cases much may be done to relieve the congestion by free venesection followed by appropriate restorative measures, such as hypodermic injections of strychnine in large doses (gr. $\frac{1}{30}$) every fifteen minutes until three doses have been taken. A warm bath, temperature 102° to 105° F., lasting for fifteen minutes; hypodermoclysis of decinormal saline solution from a pint to a quart. These measures will at times induce absorption of the œdema and prolong life. Subcutaneous injections of camphor or ether should be used. Internally we may also give camphor, wine or whiskey, and very strong coffee. Strong counterirritants should be applied to the chest, and the battery must be used. Emetics may be employed with distinct advantage if the patient's condition permits. Benzoin, liquor ammonii acetatis, enemata of senna and vinegar, or four to eight ounces of brandy with an equal amount of black coffee per rectum will at times be of service.

The postural treatment of pulmonary œdema has been advocated. This consists in having the patient lie upon his face with the head and shoulders on a lower level than the hips, thereby inviting the bronchial contents by gravitation to flow out of the mouth. When there is no contraindication this method can be tried for half an hour several times a day.

Pulmonary Emphysema—Pneumonectasia.

*Not*withstanding the many divisions which specialists make, there can be no doubt that we have an *interlobular* or interstitial and a *vesicular* or alveolar pulmonary emphysema. These two main varieties may be acute or chronic, general or local, hypertrophic or atrophic, compensating, limiting, or lobular. For practical purposes the treatment of this distressing pulmonary affliction may be divided into prophylactic and curative.

Prophylaxis.—In the treatment of emphysema one must recommend prophylactic measures to prevent any pulmonary or bronchial intercurrent disease, such as taking cold, bronchitis, hyperæmia, congestion, or pneumonia, etc., which is so liable to prove fatal in emphysematous patients. The patient must avoid overwork, straining, lifting, running, residence in cold climates, occupations in dusty, damp, and ill-ventilated places. Woollen garments with moderate exercise are recommended. A moderately dry climate, free from winds and dust, near the seashore, has proven most beneficial. The California climate is exceptionally good. Regular living must be observed. Smoking and alcoholic stimulants should be avoided. Dyspepsia and constipa-

tion must be prevented. The food should be simple, nutritious, and well prepared. Saccharine and amylaceous foods should be specially prohibited, on account of their proneness to produce flatulent distention of the stomach and bowels.

It is exceedingly important to pay particular attention to the condition of the bronchial tubes and to alleviate any bronchial inflammation. Favorable results may be obtained by the use of baths at mineral springs and health resorts, where the patient is free from his usual vocation, and where he can enjoy complete bodily rest. If he cannot go away from home, he should remain within the house during inclement weather and stay in the open air as much as possible during fair weather. Food should be given that is easily digestible. Wine, beer, and spirits should be taken sparingly. The tendency to constipation should be combated by means of dietetic remedies, such as fruit, vegetables, and graham bread, or of mild laxatives. Severe cold weather should be avoided.

Curative Treatment.—Waldenburg-Schlitzner's method of compressed-air inhalation and Geigel and Mayer's compressed-air cabinets with oxygen inhalation have been found of considerable practical benefit in pulmonary emphysema. Mechanical assistance by means of the pneumatic cabinet has also proven very beneficial. The patient is made to exhale into a rarefied atmosphere, thereby emptying the lungs of more complemental air than is expired under ordinary circumstances. An assistant may also compress the thorax twenty or thirty times per minute for several hours daily, thereby assisting the expiratory movement. Intercurrent diseases, such as congestion of the mucous membrane of the lungs, bronchitis, asthma, pneumonia, etc., should be carefully avoided. Emphysematous patients, however, frequently have some form of chronic bronchitis. For this condition medicated steam inhalations will not only prove very grateful to the patient, but also will be found to possess considerable curative properties. The following is a combination which the writer has used:

Formalin, 1:5,000 solution; thymol, 1:1,000; sandalwood oil, eucalyptus oil, and terebene, of each 1:50, in creosote water, q. s.

Steam inhalations of wine of ipecacuanha, compound tincture of benzoin, turpentine, sandalwood oil, tar, sulphurous acid gas, eucalyptol, pinol, creosote, ammonium chloride, carbolic acid, or formalin will also be found to give great relief. The patient should live in a warm climate, where the temperature does not go below 60° F. The sleeping apartments should be saturated with steam and a balsamic inhalation, such as tolu, cubebs, copaiba, terebene, or creosote, etc. Ferruginous tonics with strychnine and cod-liver oil are invaluable. The diet should be predigested, highly nutritious, and largely albuminous. In gouty or lithæmic patients colchicum or strontium is

indicated. Cardiac or renal cases must be treated symptomatically. The alimentary canal should be emptied once or twice daily, gentle open-air exercise should be employed, and the patient should live in the best hygienic manner possible. Daily massage of the chest walls and calisthenics are of value.

During an asthmatic attack there is perhaps nothing better than gr. $\frac{1}{100}$ of duboisine or atropine with a quarter of a grain of morphine used hypodermically, to be followed with full doses of ammonium iodide in chloroform water. This will often cut short an attack and produce profuse bronchial secretion and facilitate expectoration. A full dose (℥ ss.) of tincture of stramonium with a little (gr. ss.) codeine in chloroform water will also often relieve an acute asthmatic attack. Stramonium leaves smoked may at times assist. Sparteine valerianate is of special service in relieving the spasm. Arsenic, iron, and strychnine are among the best internal remedies to strengthen the lung, to stimulate the power of the heart, and to increase the red blood corpuscles. They are also excellent respiratory stimulants. Terebene, lobelia, and codeine give good results. As a general tonic there is perhaps nothing better than iron, quinine, and strychnine. Grindelia in full doses every three hours will also afford relief. To produce sleep there is nothing better than one or two full doses (gr. x.) of chloral. Strychnine is particularly valuable as a respiratory stimulant when there is constant dyspnœa with prolonged expiration. Lobelia is an excellent remedy to allay the dyspnœa which accompanies capillary bronchitis in emphysema. Cod-liver oil, hypophosphites, and chalybeates are valuable remedies to tone up the general system and to increase nutrition. Three-grain doses of suprarenal capsule powder, administered from three to six times a day, have given immediate and oftentimes permanent relief in the treatment of the asthma occasionally accompanying emphysema. Sodium benzoate with caffeine may be used with advantage in emphysematous bronchitis. Asthmatic attacks may often be instantaneously relieved by the inhalation of ten to fifteen minims of pyridine or methylene bichloride. Iodide of ethyl in six-minim capsules is much used for the same purpose in France. A few whiffs of chloroform or of ether, smoking arsenical cigarettes, or the internal use of chloral hydrate and lobelia may also overcome the paroxysm. Piperazin, five grains three times daily, has been observed to have a marked effect in reducing the inflammation of the pulmonary mucous membrane in emphysema. In pulmonary emphysema we frequently have dry bronchitis. For this condition we would recommend iodide of potassium with iodide of iron in small but continuous doses with large quantities of warm drinks, such as slippery elm, flaxseed tea, or gum arabic water (℥ i. to O i.). Ipecac and small doses of apomorphine are also of consider-

able value. In the dry bronchitis which is so frequently present, iodide of potassium, citrate of potassium, and pilocarpine will be found a valuable combination. Strychnine may be said to be of value in all forms of the disease. A mixture of potassium iodide, chloral, and lactucarium is claimed by many to be a specific in emphysematous asthma.

Paraldehyde (ʒ ss.–i.), antipyrin (gr. v.–x.), lobelia (♏ x.–xx.), grindelia (♏ xx.–xxx.), cannabis indica (♏ x.–xxx.), sanguinaria, euphorbia pilulifera, camphor, etc., have all proved efficacious in bronchial and emphysematous asthmatic attacks. It is important that all the emunctories are looked after. The pores of the skin should be kept open by means of dry hot-air baths and massage. Together with a generous diet and open-air exercise in a suitable climate, much can be done. Even chronic cases are decidedly benefited, especially in the salubrious climate of California.

Atelectasis—Apneumatosis.

Complete atelectasis is sometimes seen in extreme kyphosis. The lung in this condition is usually completely atrophied. When the left lung is involved the heart is pushed entirely into the corresponding chest cavity. When the right lung is missing the heart is displaced to the right. There seems to be complete arrest of development of the diseased lung, which shows but a small mass of fibrous tissue. In a probably unique case, recorded by C. Helbing (*Centralblatt für Pathologie*, 1898), the left lung was replaced by a large mass, weighing sixteen pounds, of absolutely airless fibrinous material which had undergone cartilaginous and calcified degeneration. The explanation offered is that it was a congenital defect of the left lung which was replaced by hypoplastic embryonic tissue.

In the *treatment* of atelectasis of the congenital variety very little can be done. The concomitant struma, inherited syphilis, or rickets must be treated on general principles with nutritious, supporting, stimulating food and iodide of iron, hypophosphites, and chalybeate tonics. In the acquired form of atelectasis or apneumatosis the cause must be discovered and remedied if possible. Calisthenics, prolonged inspirations of rarefied air surcharged with oxygen should be practised daily. Should the patient be bedridden he must be changed frequently from side to side, and he should be encouraged to make deep inspiratory efforts. Cod-liver oil with ferruginous tonics should be exhibited with the best possible food procurable. Stimulating liniments applied to the chest with scientific massage may accomplish some good. Faradization for half an hour daily over the inspiratory muscles of the neck and chest also assists in the general plan of treat-

ment. Pressure from pleuritic effusions, hydrothorax, pneumothorax, abdominal fluids, growths, or tumors must be removed. Should collapse occur during an attack of capillary bronchitis, the treatment must be directed to promote liquefaction of the secretion and to facilitate expectoration. Ammonium chloride with terebene and codeine in chloroform water and syrup will be found very efficacious. The inhalation of steam with turpentine, creosote, tar, and oil of eucalyptus will also be found serviceable. In chronic cases the balsams of tulu, copaiba, and cubebs, cod-liver oil, pure olive oil, or petroleum emulsion with ferruginous tonics, good wholesome food, pure fresh air, and sunshine and gentle exercise will accomplish all that we can hope for. The timely use of tepid baths with shower baths is a special preventive of the development of atelectasis, as forced inspiratory efforts are made whenever the cold douche is directed against the chest or the spine.

Caisson Disease—Compressed Air Illness.

Increased atmospheric pressure, to which caisson workers, divers, and deep miners are exposed, produces symptoms of paraplegia, hemiplegia, anæsthesia, and apoplectic attacks. The paralysis of the legs is the most common symptom coming on only after return to the normal atmosphere.

The most plausible theory of this disease is that there is an increase of gases in the blood due to the increased atmospheric pressure in the air cells. That this is due to carbonic-acid poisoning is not clear. It is probably due to nitrogen. In persons found dead from this disease there has been observed free gas in the finer blood-vessels with subcutaneous emphysema. The *preventive treatment* consists in keeping the atmosphere in the caisson as pure as possible. Men should not work in the cylinders longer than two hours at a time, and a large proportion of oxygen, at least thirty per cent. instead of twenty per cent., should be used. Ergotin and morphine hypodermically with sodium salicylate internally have given the best results. Inhalation of oxygen may also be useful. Venesection and transfusion with decinormal salt solution may prove beneficial in acute cases.

Lobular Pneumonia—Bronchopneumonia.

Treatment.—In acute bronchopneumonia care must be taken in the use of aconite, veratrum viride, and other depressants. The same remark applies to antipyrin, salicylates, and other antipyretics. A supporting plan of treatment should be adopted from the onset, as the disease is apt to be a lingering one, requiring all the patient's strength.

Some authorities recommend cold applications—cold baths and ice packs—in these and other cases. The cold bath acts in several ways: first, by directly abstracting heat; second, by stimulating the cutaneous circulation and glands; third, by relieving the vascular stagnation, whereby the elimination of toxins is increased; fourth, by diminishing the production of heat or thermogenesis. Advocates of this measure contend that there need be no fear that in the exanthematous fevers the eruption is "driven inward," as our mothers used to say, by cold, as experience has proven that cold baths are our surest aid in scarlatina, rubeola, and even smallpox.

We believe the cold bath, ice pack, Leiter coil, etc., have their legitimate use, and we do use them and recommend their use in selected cases—acute sthenic pneumonia, for instance; still we favor the hot dry-air treatment or hot baths and hot poultices and oil-silk jackets lined with cotton, etc. *Cold is death, warmth is life.* In acute hyperæmia, bronchopneumonia, etc., hot applications to the chest with hot dry air or moist (steam) inhalations producing profuse diaphoresis will accomplish much more for the patient than any cold application.

In young children we would advise against the use of the cold bath and the application of ice to the chest. A generous hot poultice of flaxseed meal or the oil-silk jacket lined with cotton batting will be found very much more grateful to the patient, and will accomplish much more good in the way of liquefying the congestion and assisting in the expectoration than will cold applications. Furthermore, we know from practical experience that these warm applications will do no harm, which the cold applications might do. The application of gentle massage or friction over the chest walls three or four times a day with a stimulating liniment will assist the engorgement of the lung by dilating the cutaneous blood-vessels.

The inhalation of steam impregnated with oil of turpentine or oil of cinnamon, oil of cade, creosote, etc., will be found very grateful to the patient. The early use of strychnine hypodermically or internally with a little quinine in tonic doses is probably one of the best treatments that can be instituted. Camphor in olive oil, in doses of from a quarter of a grain to one grain three or four times daily, will be found to lower the temperature and act beneficially on the mucous membrane of the lung. Sanguinaria, serpentaria or senega, ammonium carbonate, and digitalis may be used with benefit in certain adynamic cases. Terpin hydrate and bryonia in small doses with codeine and belladonna have been used with considerable success. Chlorate of potassium is a good expectorant. The iodide of ammonium with arsenic and strychnine will stimulate the respiratory action and increase liquefaction of the secretion and aid in its expectoration.

Heroine diminishes the desire to cough. Iodide of ethyl with oil of gaultheria is very valuable as an inhalation in hot dry air.

Apomorphine, gr. $\frac{1}{10}$ hypodermically, is not only an excellent expectorant, but is also a powerful hypnotic, producing refreshing sleep. Douglass, in *Merck's Archives*, has shown that it is a safe hypnotic, free from disagreeable after-effects if given in the proper dose. A saturated solution of boric acid will neutralize both the hypnotic and emetic properties of apomorphine.

An excellent demulcent expectorant is made of linseed oil, Irish moss, glycerin, and minute doses of hydrocyanic acid, chloral, and dionine. Dionine is ethyl-morphine-hydrochlorate. It relieves the cough and increases the expectoration. It is given in one-eighth and one-quarter-grain doses every three to six hours. Eosote or the valerianate of creosote is also a valuable remedy in bronchopneumonia as a stimulating expectorant. Thiocol, the potassium-guaiacol-sulphonate, in fifteen-grain doses is of service in bronchopneumonia. Geosote, the guaiacol valerianate, is another remedy of much value. Camphoric acid in ten- to twenty-grain doses in the early stage of an attack of bronchopneumonia will ameliorate the attack and at times abort it. Iodoform vasogen and creosote vasogen are of considerable value in allaying the cough and assisting free expectoration. Heroine in half-grain doses is one of the best sedatives we have for the cough in dyspnœa. It also assists expectoration. Euchinin is another safe antipyretic given in the same dose as quinine. The free inunction over the chest of unguentum Credé or the soluble metallic silver is claimed to abort an attack of pneumonia. Brilliant results have been obtained by the administration of pure carbolic acid. The acid is freely eliminated by the mucous membranes of the bronchioles and bronchi. Drachm doses of a three-per-cent. solution is given every two to four hours. It is a sedative to the respiratory tract, increases secretion, favors expectoration, and is one of the best antiseptics for the lungs we possess. A one-per-cent. solution of arsenic in five-minim doses is recommended in the subacute stage. Tincture of musk is an excellent respiratory tonic. Sparteine has proven of great value in bronchopneumonia. Naphthalin, tar, eupatorium may also be of value. Nuclein renders the blood more bactericidal. Hyperleucocytosis with its concomitant phagocytosis is the most potent means of warding off inroads of microorganisms that once find their way into the blood, as in septicæmia, septic pneumonia, etc.

Intravenous saline injections of decinormal salt solution injected under the skin or into each mammary gland increase the amplitude of respiratory undulations of blood pressure, and by increasing the pulmonary circulation favor the absorption of the serous transudation in the bronchi.

Chronic Pneumonia (Interstitial, Cirrhotic, Fibrous).

In the *treatment* of chronic pneumonia, the so-called interstitial or fibroid phthisis, great care should be exercised to prevent the recurrent attacks of catarrhal inflammation of the mucous membrane. The treatment should be in a great measure prophylactic. Patients with chronic fibrosis of the lung should live in a warm equable temperature. The temperature of the patient's room in which he sleeps should never be below 60° F., and he should exercise in the open air at a temperature not below 60° F. if possible. His occupation should be in the open air where he can be free from dust and bad ventilation. The bodily strength should be maintained at its highest point of excellence.

Heavy lifting, straining, and running should be prohibited. The patient should be required to take four meals a day of highly nutritious or predigested food-stuffs. Strychnine, ferruginous tonics with cod-liver oil, petroleum, or olive oil should be given with every meal. Pure California olive oil is one of the best tissue builders we know of. It is more easily taken than cod-liver oil. It digests and assimilates rapidly, and we have used it with decided benefit in many of the wasting diseases. Emulsions are readily made with the yolk of an egg, olive oil, and gum arabic. The writer's plan is to give from half an ounce to an ounce of pure olive oil one hour after each meal. Even infants thrive on pure olive oil. Linseed oil is also a valuable food and sedative expectorant. The cough in chronic pneumonia may require some mild expectorants. The hæmoptysis, if present, may require astringents or hæmostatics such as gelatin and iodide of calcium; otherwise the patient must be treated symptomatically. High altitudes should be avoided; a low humid climate, such as is found on the Pacific Coast from San Francisco to San Diego, is most conducive to the welfare of these patients. Should the expectoration be profuse, balsams of tolu, cubebs, copaiba, oil of cade, turpentine, oil of mountain pine, with minute doses of atropine and dionine, will be found to act most beneficially. Excellent results are obtained from the administration of gr. $\frac{1}{24}$ of hydrochlorate of heroine hypodermically. Myrtol, in doses of from five to fifteen minims in an emulsion, has been successfully employed in cases of catarrh and bronchorrhœa. For sleep, such remedies as chloral hydrate, butylchloral in five-grain doses, sulfonal or trional in ten-grain doses, or paraldehyde in fifteen- to thirty-minim doses can be safely recommended.

Brown Induration of the Lungs.

In *treating* brown induration of the lungs, the first consideration is that of relieving the patient from the cause if possible, then to stimulate the heart and lungs with nutritious diet, ferruginous tonics, strych-

nine, and digitalis. Stimulating expectorants may be required. Arsenic and quinine will be found to be excellent adjuvants. Calisthenics and gentle outdoor exercise are to be recommended.

Pyæmia of the Lungs.

Treatment.—In these days of modern antiseptic surgery one seldom sees a case of pyæmia of the lungs. Prevention here is truly worth much more than an attempt to cure. Should a patient be so unfortunate as to contract pyæmia of the lungs, the prognosis must of necessity be very serious. We do not hesitate nowadays to open one or more large abscesses in the lungs, nor indeed to do a pneumonectomy, but of course it would be impossible to reach the smaller multiple abscesses throughout the lung and to evacuate the pus during the lifetime of the patient. In such cases we should endeavor to treat them antiseptically by means of inhalations of formalin, thymol, oil of cloves, creosote, turpentine, etc. Cold applications to the chest may exert a beneficial influence. Tonics should be given early in the disease. For internal medication there is perhaps nothing better than tincture of steel in ten to thirty minim doses, with one-fiftieth grain of bichloride of mercury given in glycerin and water every three to six hours. Sodium sulphocarbolate has proved efficacious in ten-grain doses every four hours. Permanganate of potassium in grain doses every three hours may be useful. Otherwise pyæmia must be met by stimulating treatment to support the patient's strength. Antipyretics may be required but are of doubtful utility. Perhaps quinine is the only exception. A useful spray deodorizer is composed of formalin, ♏ i.; essence of thyme, ♏ v.; eucalyptol, oil of gaultheria, terebene, and creosote, of each ʒ i.; and glymol, q. s. ad ℥ iv. Sig.: Use with atomizer for inhalation.

Should the abscess be single and within reach, surgical interference is the only possible chance of a cure. Injections into the abscess cavity of pure carbolic acid, 1:2,000 formalin, iodoform (ten per cent.) emulsion, two-per-cent. protargol have given promising results in suitable cases. Many brilliant results have been obtained during the last year by the resection of a rib or two and the evacuation of abscess cavities of the lungs with or without pneumonectomy.

Gangrene of the Lungs—Pneumocace.

Gangrene of the lungs is now fortunately becoming one of the rare diseases. In its *treatment* very little can be done besides administering abundant nourishment and stimulants in the form of soups, broths, carbonate of ammonium, Hoffman's anodyne, strychnine, aromatic spirit of ammonia, tincture of iron, quinine, whiskey, etc. Antisep-

tic inhalations have also been found beneficial. For this purpose formalin, creosote, terebene, oil of cinnamon, oil of gaultheria, oil of cade, etc., with pure oxygen, have proven most serviceable. The internal administration of sulphocarbolate of zinc, bichloride of mercury, chloride of calcium, with stimulating expectorants, may prove beneficial. In gangrene of the lungs one should watch for bulbar paralysis, so that food may not enter the trachea. When deglutition is difficult the patient should be fed by the stomach tube. Myrtol with turpentine, eucalyptol, sandalwood oil, or terebene in an emulsion is an excellent remedy to prevent fetor of the breath. Formaldehyde inhalations have appeared to lessen the expectoration as well as to deodorize the breath. In septic cases alcoholic stimulation is absolutely essential. Cod-liver oil, hypophosphites, and bitter tonics are good. Food should be given as often as every three hours if the patient can take it. When the gangrenous cavity is distinctly localized and near the surface, resection of a rib may be indicated and pneumonectomy performed, or injections of antiseptics may be made directly into the gangrenous cavity. For this purpose creosote, ♏v., in a drachm of glycerin, or ten-per-cent. iodoform emulsion has been used; 1:2,000 formalin in decinormal salt solution, pure carbolic acid, have also seemed to do some good. Opening, scraping, draining, and disinfecting the cavity are also to be considered. A number of cases are on record in which this latter method has proven successful. Energetic inunction with mercurial ointment is sometimes of service. Good results have been reported from the intrapulmonary injection of 20 c.c. of a 1:4,000 solution of bichloride of mercury.

Malignant Diseases of the Lungs.

Primary malignant disease of the lungs is exceedingly rare. The disease is usually transferred from other parts of the body or by direct extension from the breast, the pleura, the mediastinum, or the œsophagus. Secondary cancerous growths are usually multiple and scattered throughout both lungs. Most frequently we have carcinomata, next sarcomata, and rarely enchondromata.

Diagnosis.—The patient usually complains of difficulty in breathing, with a sense of heaviness and weight in the chest. Cough is frequent and paroxysmal in character. When the tissues are broken down the expectoration may resemble brown mucus with blood. Occasionally we have hæmoptysis. According to the location of the malignant growth there may be pain in the tracheal plexus or hoarseness on account of the involvement of the recurrent laryngeal nerve. Neuralgic or stitch-like pain indicates the involvement of the pleura. The axillary glands may be enlarged. The veins of the neck

may be swollen. There may be more or less pleuritic effusion with the general constitutional signs of anæmia, cachexia, and gradual loss of flesh and strength. The duration of life is rarely more than twelve months.

In the *treatment* of malignant growths in the lungs, such as carcinoma, sarcoma, etc., very little can be done. Fortunately primary cancer of the lung is exceedingly rare, and unfortunately secondary deposits usually involve both lungs. In malignant diseases of the chest walls, the breasts, etc., great care should be taken to prevent the direct extension of the disease into the pleural cavity and lungs. When we have miliary disseminated pulmonary cancer, its diagnosis is exceedingly difficult until the tissues begin to break down. When surgery cannot assist us in the treatment of malignant diseases of the lungs, medication should be directed to maintaining the strength of the patient.

The serum treatment by the mixed toxins of the streptococcus of erysipelas and bacillus prodigiosus has been tried. but with doubtful results.

Syphilis of the Lungs.

Pulmonary lesions of syphilitic origin occur in the late stages of the disease and in hereditary cases. As a rule they are associated with other manifestations of syphilis. Excluding tuberculosis, tumors, and aortic aneurysm, in cases of obscure lung diseases, especially when there is a probability that the patient may have been infected with syphilis twenty or forty years before, it should always be deemed advisable to push the iodide of sodium with or without mercury. In many obscure cases the antisyphilitic treatment will clear up the diagnosis and materially benefit the patient. The bronchial lymphatic glands may cause pressure symptoms leading to dyspnœa. Gummata of the lung may exist without being recognized clinically, and a sharp antisyphilitic régime with proper heart and ferruginous tonics may clear up any obscure lung symptoms. Nothing can be added to the treatment indicated for syphilis in the volume of 1896. The specific remedies should be pushed to their fullest extent—fifty to one hundred grains of the iodide daily. Iodide of sodium will be borne better than the iodide of potassium. Arsenic is a valuable adjunct, as are strychnine and ferruginous tonics.

Bronchadenitis.

Inflammation of the bronchial lymphatic glands requires about the same treatment that adenitis would in any other part of the body. The alteratives and restoratives should be given freely. Carbonate of cre-

osote with iron and arsenic are perhaps the best remedies at our command. Iodide of iron with hypophosphites and strychnine is a favorite prescription of the writer. Carbonate of guaiacol and valerianate of creosote have also been extolled. Pure olive oil will be found beneficial, as will a diet largely composed of fresh fruit and vegetables. Iodipin, the triglyceride of iodine with sesame oil, and iodide of arsenic have given good results.

Diseases of the Lungs in Association with Other Diseases.

Rheumatism.—In a résumé on page 104 of "Pulmonary Consumption, Pneumonia, and Allied Diseases of the Lungs," by Dr. Thomas J. Mays, of Philadelphia, he states that: "It appears that typhoid fever, diphtheria, scarlatina, measles, whooping-cough, mumps, influenza, and cerebrospinal meningitis have the following characteristics in common: (1) They owe their existence to the operation of specific poisons on the human organism; (2) these poisons exert a decided destructive influence on the nervous system; (3) over and above this general influence on the nervous system they show a well-defined affinity for the special nerve tract which controls the respiratory organs; and (4) pulmonary diseases are some of their most constant sequelæ." We do know that alcohol, for instance, produces its specific influence on the lung tissue and the blood-vessels as well as on the heart, kidneys, liver, etc. Syphilis also in a similar manner produces diseases of the lungs. No doubt many attacks of bronchitis are due directly to rheumatism of the lungs. If we have rheumatism and gout of the stomach, of the intestines, of the urinary bladder, etc., why may we not also have rheumatism of the lungs? In point of fact, many cases of bronchitis, to cite a specific example, will recover more quickly when treated vigorously with salicylates than under any other system of treatment. Whenever the writer sees a case of acute tonsillitis, his first prescription is salicylate of sodium in large doses. This will abort an attack of tonsillitis in the course of a day or two, showing undoubtedly rheumatic influence on diseases of the tonsil. Similarly, when a rheumatic or a gouty patient gets an attack of bronchitis, the salicylates and wine of colchicum or both will abort the attack. In asthmatic attacks we frequently find the salicylates do more to ameliorate or stop an attack than any other form of treatment we know of, arguing clearly that the attack must depend largely, if not entirely, upon the rheumatism poison, whether that be uric acid, lactic acid, chemical toxins, or microorganisms. It were well then for the practitioner to bear in mind the existence of bronchial and pulmonary rheumatism and to treat the patient accordingly.

Beriberi.—One of the early symptoms of beriberi is hyperæmia of the mucous membrane with œdema of the bronchial tubes at the bases of both lungs. The bronchioles are generally filled with frothy fluid. With this we find emphysema of the apices. This distention of the lungs which has been observed in the Orient is ascribed by Schube to degenerative changes in the vagus. This embarrassment of the pulmonary innervation must be looked upon as one of the fatal terminations of beriberi. Few cases of beriberi terminate fatally unless the pneumogastric nerves have been involved. In the treatment of beriberi, which we see frequently on the Pacific coast, methylene blue given in full doses, gr. ij. to v. three times daily, induces rapid amelioration of all the symptoms. In cardiac and pulmonary complications, strychnine, digitalis, or strophanthus is indicated. Full doses of nitroglycerin will abate acute cardiac distress. Nitrite of amyl by inhalation will ward off a cardiac attack. Inhalation of oxygen is also useful. Sulphate of sodium in small repeated doses to counteract the universal constipation with resultant autointoxication has proven very beneficial. Sulphur with strychnine and cannabis indica produced prompt relief in a number of cases treated recently by the writer. One-fiftieth of a grain of bichloride of mercury with thirty minims of the tincture of chloride of iron given in glycerin and water every three hours improved three sailors so markedly that they were able to resume their voyage inside of a month. The diet should be changed from the non-nitrogenous to the nitrogenous. Fresh animal food should be taken freely with fresh milk, eggs, and fresh vegetables. Strychnine, arsenic, and iron have also contributed to the elimination of the disease process.

Diabetes.—From the close proximity of the diabetic centre and the respiratory centre, as Dr. Mays points out, there is good physiological ground for believing that gangrene of the lungs is one of the fatal terminations of diabetes. Brunton states that pneumonia and tuberculosis also frequently occur in diabetic patients.

Leprosy.—Hillis, quoted by Mays, states that lung complications occurred in seventeen per cent. of his cases of tuberculated leprosy, with special proneness to pulmonary tuberculosis. Among the many symptoms pointing to involvement of the mucous membrane are ozæna, hoarseness, aphonia, and the signs of inhalation-pneumonia. In the treatment gurjon oil and chaulmoogra oil have been employed with the most pronounced beneficial results. Arsenate of iron, nitrate of silver, ichthyol, chrysarobinum, europhen, oil of cashew, Hoang-nan, thyroidin are among the remedies employed with uncertain benefit.

Pneumoactinomycosis.—When the lung or pleura is involved, the infection may be secondary to the neck or jaw, or it may result from a primary infection through the bronchi. The tendency of actinomycosis starting in the lung is to make its way outward and to involve

the pleura, chest wall, and skin. This is frequently noted in man. The progress is a slow, insidious one, but progressive, and unless surgery can step in and help us there is little that can be done excepting that of supporting the patient.

Glanders.—Glanders nodules have occurred abundantly in both lungs in some recent cases of the disease we have had in California. The glanders was transmitted in each case from horses. Numerous nodules were scattered over the surface of the body and granulomatous ulcerations were found in the mouth, nose, and larynx, with abundant nodules in both lungs. In all of these cases the characteristic bacilli mallei were demonstrated. Death occurred in seven to nine days. The treatment for glanders in man should be as it is in animals, with large and heroic doses of iodide of potassium. Two to four drachms should be given every twenty-four hours, with large quantities of water, together with iron, quinine, and strychnine supporting treatment. This is claimed by our veterinarians to be the rational treatment of glanders. Surgical treatment should be instituted within the first twenty-four to forty-eight hours, viz., cauterization and sterilization of the infected nasal and oral mucous membranes.

Bubonic Plague.—Besides the ordinary varieties of bubonic plague, *pestis major* and *pestis minor*, the lungs are frequently involved. There are a sharp chill, stabbing pains, cough, high temperature, and rapid consolidation with rusty sputum. It is supposed that the *bacillus pestis* is inhaled and rapidly absorbed, setting up intense hyperæmia which soon goes on to true inflammation and complete consolidation. From the time of exposure to that of death is only a matter of from three to five days. The treatment consists in Haffkine's prophylactic serum before exposure and Yersin's curative serum after exposure. Generous supportive treatment should be instituted from the onset, as the plague pneumonia is fatal in ninety per cent. of all cases.

DISEASES OF THE ŒSOPHAGUS.

BY

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Œsophagoscopy.—Although the use of the œsophagoscope has strongly been advocated within the past few years, especially by Rosenheim and most recently by Gottstein [1] and F. Kraus,[2] the objections to its employment are such that œsophagoscopy has found but little favor except in the hands of those especially skilled and experienced.

The introduction of the instrument is difficult for the inexperienced physician, and impossible in a number of cases even in the hands of the skilled, is distressing to most patients, dangerous and even fatal in certain instances, and in others has either given no information or led to errors of diagnosis. It is inadvisable in a considerable proportion of diseases of the œsophagus and unnecessary in some of the gravest diseases of the gullet.

The advantages claimed for it are that it furnishes a means of exact diagnosis of certain affections, that it permits the ready removal of some foreign bodies from the lower end of the œsophagus, and that by means of it dilators may be introduced into strictures otherwise inaccessible. Furthermore, it has been found by Rosenheim that when the entrance to strictures has once been reached, the passage of dilators has subsequently been possible without their insertion through the œsophagoscope.

Roentgen Rays.—The value of the Roentgen rays in determining the nature of certain affections of the œsophagus has been shown by Schwörer [3] who by means of them was enabled to recognize and outline the seat and position of a dilatation of the œsophagus. A tube containing a copper wire was passed through the œsophagus into the stomach. Through a second tube introduced into the œsophagus were poured 30 gm. of bismuth suspended in 300 c.c. of water. With the fluoroscope a shadow was seen corresponding to the dilated œsophagus in which the presence of the copper wire was dimly recognized, but the outline of the wire was more sharply defined below the diaphragm,

where it lay in the stomach. Blum [4] determined the seat and form of an œsophageal diverticulum also by means of bismuth and the Roentgen rays. In his patient 50 c.c. of mixture containing five per cent. of subnitrate of bismuth were used. The site, length, and width of a stricture of the œsophagus were ascertained by Holzknecht [5] also by means of bismuth and the fluoroscope.

Diagnosis and Treatment of Fibrous Strictures.—The value to be attached to the œsophagoscope in the diagnosis of stricture of the œsophagus has previously been mentioned. The methods of dilatation are those used in the treatment of urethral strictures. Local sensitiveness may be blunted by the use of cocaine, ten-per-cent. solution, or of eucaine, three-per-cent. solution, applied directly to the sensitive part by means of a syringe attached to an œsophageal tube as recommended by Rosenheim. The œsophagus is to be cleansed with lime water or a salt solution through a single or double œsophageal tube. An ounce or more of oil may be swallowed or poured through the tube to facilitate the passage of the sound. If the ordinary œsophageal bougie fails to enter or pass through the strictured portion, the flexible, spiral, metallic sound, recommended by Rosenheim, may be used. Zeehuisen [6] succeeded in dilating a fibrous stricture by means of silver balls, 2 to 7 mm. in diameter. The smallest was strung on a thread and swallowed at bedtime, the end of the string being attached externally. On the following day the ball was withdrawn from the stomach, having passed through the stricture, as was made apparent by the resistance offered and the reaction of the moistened knot to Congo paper. Gradually the larger balls were used, and eventually a tube of considerable size entered the stomach.

If these measures fail, attempts to dilate the stricture may be made by the passage, with or without the aid of the œsophageal tube of dilators of increasing calibre. If solid, these may be expansile, as catgut and laminaria; or the dilators may be hollow and elastic, as rubber tubing, which may be distended with air or water. Care is to be taken that expansile dilators are removed after fifteen or twenty minutes, and that distensible dilators should not be too powerfully stretched. On this subject, see a recent communication of Starck.[7]

Diagnosis and Treatment of Dilatation.—The use of the Roentgen rays in the diagnosis of dilatation of the œsophagus has previously been mentioned. Strauss [8] had a patient who learned that it was easier to swallow nourishment after previously drinking carbonated liquids. The former found it facilitated the passing of a tube into the stomach through the dilated œsophagus to attach a rubber bag to the mouth of the tube and force air through the latter as it reached the diaphragm. Beneke [9] observed that his patient with diffuse dilatation of the œsoph-

agus could more readily swallow soft or liquid nourishment after first drinking and regurgitating ten or twelve glasses of water.

Differential Diagnosis of Diverticulum and Dilatation.—Strauss[8] suggests that in simple dilatation of the œsophagus it is easy to inflate the stomach through an œsophageal tube without discomfort, while if the tube lies in a diverticulum inflation does not facilitate the advance of the tube and causes distress.

Schwörer[9] passed a tube, the lower third of which contained several openings, into the stomach, and another into the œsophagus until its progress was arrested. He then poured fluid into the latter, but none could be siphoned through it, indicating that the fluid had not entered a diverticulum, but had passed from the dilated œsophagus through the fenestrated tube into the stomach.

For the differential diagnosis between dilatation and diverticulum Zweig[10] recommends the introduction of a stomach tube, which usually enters the diverticulum. Another tube is then passed into the stomach, where its presence may be determined by the expression through it of gastric contents. A solution of methylene blue, somewhat less in quantity than that of the fluid previously removed through the first tube, is poured into it. The tube in the stomach is gradually withdrawn. If there is a simple dilatation the methylene-blue solution will escape as the tube enters the œsophagus. If, on the contrary, there is a diverticulum, little or no fluid will flow through the tube on its withdrawal through the œsophagus from the stomach.

Curved sounds, or those with a tip bent at an angle, have been used successfully in finding the opening of a diverticulum.

Treatment of Cancer of the Œsophagus.—It is generally admitted that no attempt should be made to overcome, by means of a sound, a cancerous obstruction of the œsophagus until there is considerable, if not complete, inability to swallow liquids. Milk, however, may form curds, and thus obstruct when other liquids can enter the stomach. Rosenheim is convinced that the large majority of cases of malignant disease of the œsophagus are not suitable for treatment with the sound.

If the use of this instrument is productive of no benefit, or distressing or injurious, recourse must be had to rectal feeding unless gastrostomy be preferred.

The use of permanent cannulæ in the strictured portion of the œsophagus has generally been given up because the tube frequently becomes obstructed with food or cancerous growth, the attached threads have been separated and the removal of the tube rendered difficult, and the tube when long in position has tended to cause suffering and promote sloughing of the tissues. At a discussion upon this subject in the Berlin Medical Society[11] von Leyden, one of the earliest advocates of their use, stated that despite the immediate relief often obtained, he

no longer used them since the benefits were not compensated for by the harm done. Ewald considered the ability to swallow usually better without than with the permanent cannula. Rosenheim saw no especial benefit from its use. Similar views were held by Renvers and A. Fränkel.

Curschmann,[13] on the contrary, still advocates the use of the cannula in selected cases.

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DISEASES OF THE STOMACH.

BY

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NEW YORK.

IT is about six years since the article on this subject was published in Vol. VIII. of the present work. In this supplementary article I shall endeavor to discuss what there is new that has been brought out in the interval.

Methods of Examination.

The amount of HCl and in most instances also that of the total acidity can be approximately gauged[1] by means of a strip of paper saturated with a one-half-per-cent. dimethylamido-azo-benzol solution. A minute quantity of stomach contents is placed by means of a glass rod upon a strip of dimethylamido-azo-benzol paper (0.5 by 8 cm.). If the paper turns red, one drop of the contents is diluted with two drops of water in a small porcelain dish. A glass rod is dipped into the mixture and the test paper again touched. If it still turns red, one or two more drops of water are added and the procedure is repeated as before. This is done until only a slightly red or almost no red color is produced by the mixture upon the test paper. In this way the amount of dilution required for a trace reaction with the test paper is determined. It is clear that the more HCl there is in the stomach contents the more they can be diluted, still giving a trace reaction with the dimethylamido-azo-benzol paper. A dilution of from 3 to 6 would correspond to a normal, under 3 to a subnormal acidity, and over 6 to hyperacidity.

The numbers given refer to the examination one to one and one-half hours after Ewald's test breakfast. If we have to test after other more complicated meals (test dinner, etc.) hyperacidity would be indicated by somewhat smaller amounts of dilution (from about six times on), since we estimate approximately only the free HCl and the amount of the latter is relatively small after meals containing much albumin.

The method just described of approximately determining the quantity of free HCl in the stomach contents will be of value in the

following two conditions: (1) In examinations with the stomach bucket, or when from other causes only small quantities of gastric contents are at our disposal. (2) In cases in which it is of importance to obtain at once an idea regarding the amount of acidity, and the necessary solutions for titration are not at hand.

A new method of testing the acidity of the stomach contents has been devised by E. K. Dunham.[3] It consists in having the patient swallow a thread colored with litmus, congo, or dimethyl-amido-azo-benzol. Thirty inches of thread, with a small tassel attached to the end, can be swallowed with from 10 to 30 c.c. of water; a quantity too small greatly to dilute the contents of the stomach and probably not sufficient materially to modify qualitative tests.

The apparatus required is very simple; a thread, preferably of silk, a cylindrical reel of wood about half an inch in diameter, a glass tube of small calibre, and a small tassel of test threads colored with the desired indicators. The tassel is tied to one end of the thread, which is about thirty inches long. The free end of the thread is then passed through the glass tube, tied to and then wound upon the reel, the tassel being made just to engage in the opening of the tube. This reel is then floated upon water in a glass, the tassel end of the tube placed well over the arch of the tongue, and the water drunk through the tube in small, quick swallows. The end of the tube which dips into the water should be kept well below the level of the reel, otherwise the thread, in passing into the tube, will draw the reel against the end of the tube and cause too much friction.

When the act of swallowing has unwound all the thread on the reel, the free end is detached from the reel and the tube removed from the mouth. The thread should not be withdrawn from the stomach in less than three minutes, and it is better to let it remain there for five minutes. After removal, it should not be washed lest the original color return to the threads dyed with dimethyl-amido-azo-benzol.

A new test for lactic acid has been suggested by Arnold.[3] The test solution consists of two reagents: (1) A solution of gentian violet (0.2 c.c. saturated alcoholic solution in 500 c.c. distilled water), and (2) 5 c.c. of the tinctura ferri perchloridi, U. S. P., diluted with 20 c.c. distilled water. A drop of the iron solution strikes a blue color with 1 c.c. of the gentian violet, which changes to a green or yellow-green when a few drops of gastric contents, containing lactic acid, are added.

The Occurrence of Mould in the Stomach.

The part which microorganisms (bacteria and mould fungi) play in the occurrence of pathological processes in the stomach has been variously interpreted by authors. Most clinicians ascribe no special

significance to them. Others, however, assign them a prominent place; thus, for example, Talma maintains that the fermentation of carbohydrates induced by microorganisms is the cause of hyperchlorhydria; others, again, place stress not so much upon the variety of these microbes as upon their ultimate number. Among these authors Naunyn may be especially cited.

The mould fungus, as such, has been but little mentioned in the domain of gastric affections.

In all the literature the scant references to mould fungi in the stomach relate to the findings of microscopical examinations. Mould itself, recognizable by macroscopic examination, has, according to my

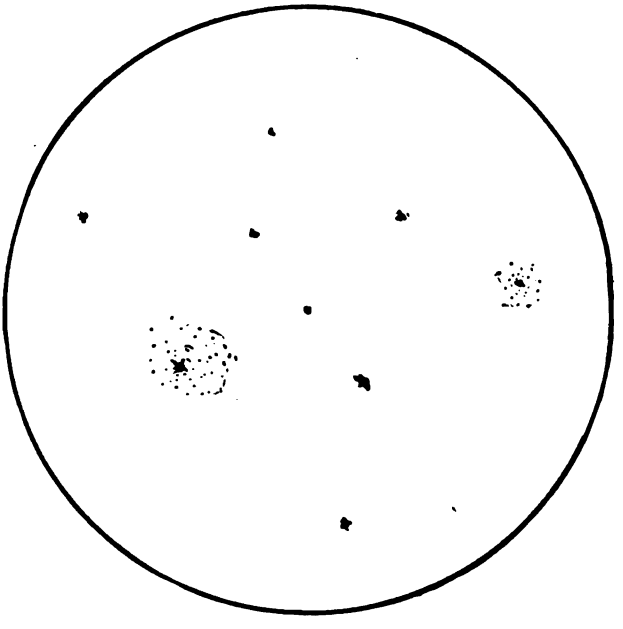

FIG. 29.—Small Pellicles of Mould found in the Stomach. (Natural size.)

knowledge, not as yet been observed clinically in the stomach. At any rate, no mention of this occurs in the literature. I have had occasion to observe several cases of mould formation in the stomach.[4] In the cases under my observation there were found in the wash water of the empty stomach small, sometimes blackish-gray, and sometimes brownish-green flakes, 2 to 5 mm. in diameter, in varying number (four to fifty and more). The microscopical examination showed that these flocculi consisted entirely of spores and mycelia and scarcely anything else. Similar flocculi were found in the same patients in the gastric contents after a test meal, and the microscope showed the same picture as in the flocculi from the empty stomach.

Sometimes these blackish-gray masses are embedded in mucus. We then note besides these fungus colonies, mucous corpuscles and numerous epithelial cells. This indicates an intimate connection between the fungus colonies and the surface of the mucous membrane. The former must adhere quite closely to the latter and perhaps even proliferate into the epithelial layer. This firm adhesion must be assumed for the reason that, if the fungi were only an accidental admixture of the ingesta, that is introduced with the latter and then carried further onward, without there being any fungus proliferation, then they would be encountered only in the gastric contents.

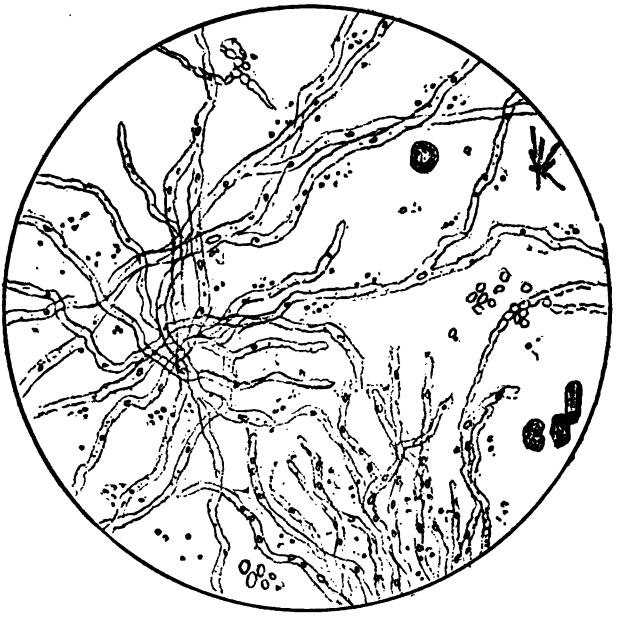

FIG. 30.—A Greenish Pellicle found in the Wash Water of the Stomach, in the fasting condition. Mycelia, free spores, and a few crystals are visible. × 240.

That the grayish-green or grayish-black flakes, which were found, represented mould pellicles, was established beyond doubt by the microscopical examination. An extremely large number of spores and mycelia was always observed. In all my cases the microscopical picture was the same, and it can therefore be assumed that the mould fungi present belonged to one and the same species.

What significance have these mould fungi in gastric pathology? Although isolated fungi may exist in the stomach for a short time without any detriment, they do not find in the normal organ favorable soil for further development. They are intimately mixed with the chyme and are carried onward, living or dead, through the pylorus.

Entire colonies of fungi which are macroscopically perceptible are probably never to be found in the normal stomach. Any considerable growth of mould would be possible only if a colony of the fungi had infested a fold of the surface of the gastric mucous membrane and had become so firmly adherent that they were not carried along with the onward passage of the chyme. Under these circumstances a fungus colony may grow undisturbed, and considerable areas of the gastric mucosa may become covered with mould. In the above-described cases such a condition must have prevailed. In lavage of the stomach the inflowing current of water exerts considerable force and tears many mould islets from their bases, so that they then appear in the wash water.

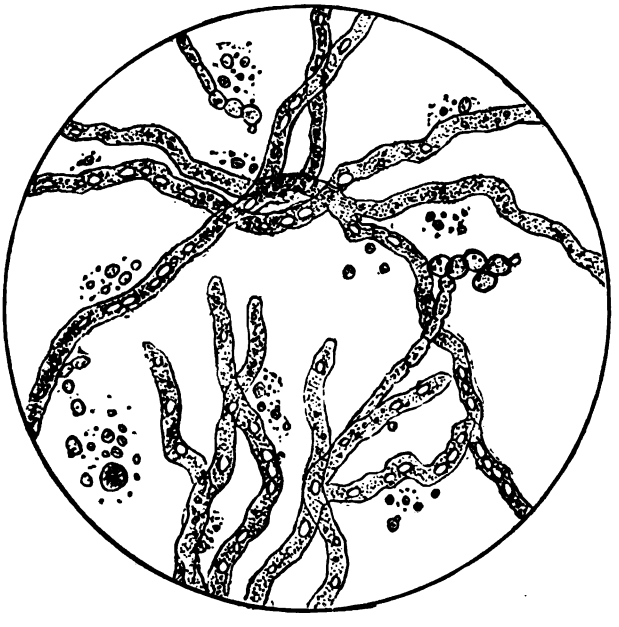

FIG. 31.—Same as Fig. 30, highly magnified. × 420.

It is scarcely conceivable that such a mould coating of certain zones of the gastric mucosa can be unattended with disturbances of the functions of the organ. Conditions of irritation as well as inflammatory processes might be expected *a priori* from the mechanical action of the mould.

After these theoretical conclusions it would be profitable to analyze more closely the cases that have been described, and to determine whether the mould formation was in a causative relationship to the symptoms of the disease. The decision of this question is, however, very difficult, because *post hoc* is not always *propter hoc*. I have

met with the mould formation particularly in two groups of gastric affections: first, in cases of intense hyperchlorhydria (occasionally attended with hypersecretion and vomiting); and, second, in gastralgia with normal or reduced gastric secretion. It cannot be denied that in many of these cases the mould flakes became smaller in number or disappeared after gastric lavage followed by spraying with a one- to two-per-mille solution of nitrate of silver. In connection with this a subjective improvement could be observed in the condition of the patient. Yet it cannot be said with certainty that the mould produced the existing pathological process in the stomach; for we find cases analogous in every respect without the presence of mould fungi. Notwithstand-

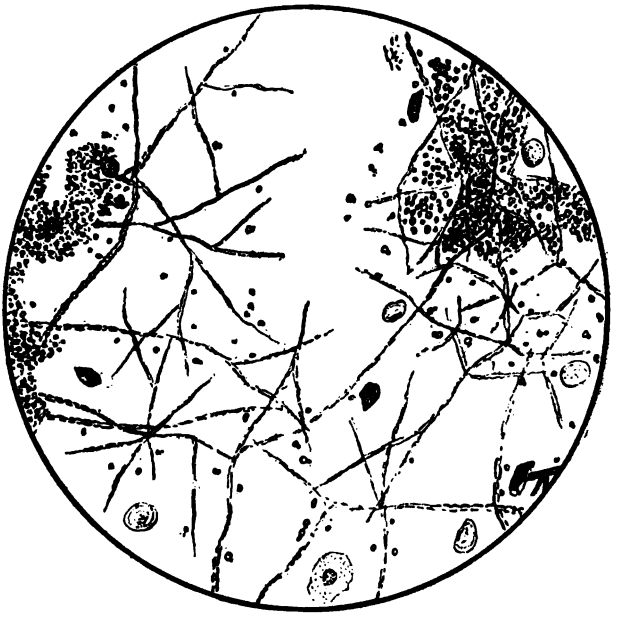

FIG. 32.—A Blackish Pellicle found in the Gastric Contents after a Test Breakfast. Numerous spores, mycelia, a few crystals, starch granules, and epithelial cells are visible. × 140.

ing this, it appears plausible that these mould fungi are connected to a certain extent with the above-mentioned abnormal conditions; and even if they are not the cause of these, they undoubtedly increase their severity.

The occurrence of mould in the stomach in large masses must, therefore, be considered of importance from a therapeutic standpoint; hence it must be our endeavor to free the stomach from them as soon as possible. This is best done by irrigation of the stomach in the fasting state of the patient. This acts in a purely mechanical manner, since the mould flakes are removed with the water. The use of the

gastric douche might also have a favorable influence in this direction. Following this the application of an antiseptic solution of silver nitrate with a spray appears likewise of some utility. Aside from the therapeutic measures just described, the treatment of these cases must be directed in accordance with the special disease present.

Œsophagoscopy.

Œsophagoscopy in the diseases of the œsophagus and cardia has gained an important place in the last few years. All the literature of importance on this subject will be found in an article[6] published by

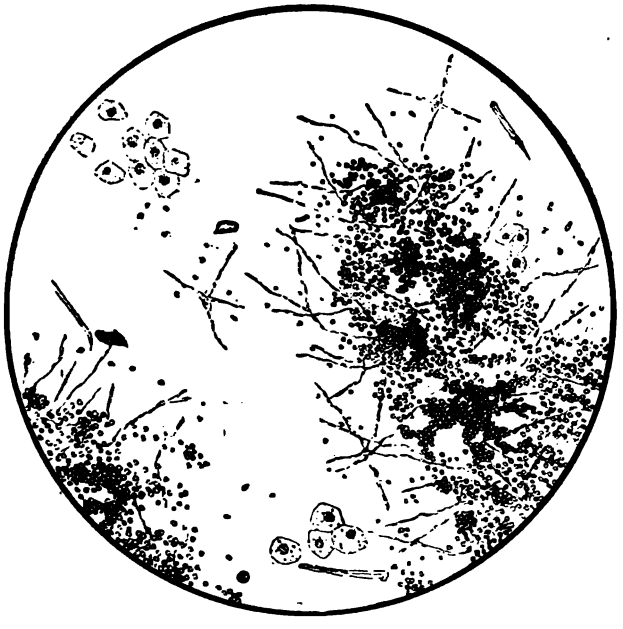

FIG. 33.—A Blackish Pellicle found in the Wash-water of the Stomach, in the Fasting Condition. Numerous spore colonies, mycelia, a few crystals, epithelial cells, and several algæ are visible. × 120.

me in the year 1897 regarding the inspection of the œsophagus and cardia. Further important papers on œsophagoscopy are those of von Hacker[6] and Rosenheim.[7] Von Hacker's epoch-making labors show most plainly the high and practical value of this method of examination, which not only facilitates the diagnosis of many of the diseases of the œsophagus, but frequently exerts a direct influence upon their treatment.

In the instruments used up to now for œsophagoscopy (Mikulicz, Rosenheim, Kelling) the source of the illumination is outside of the œsophageal tube. As a rule, the panelectroscope is employed for this

purpose—an instrument that throws concentrated light through the whole tube, thus illuminating the lowest spot that is to be inspected. It is evident that inspection would be easier if the lamp were placed at the lower end of the tube near the area to be examined, since a better illumination could in this way be secured. With the appearance of the so-called "cold lamps" this principle could be practically executed.

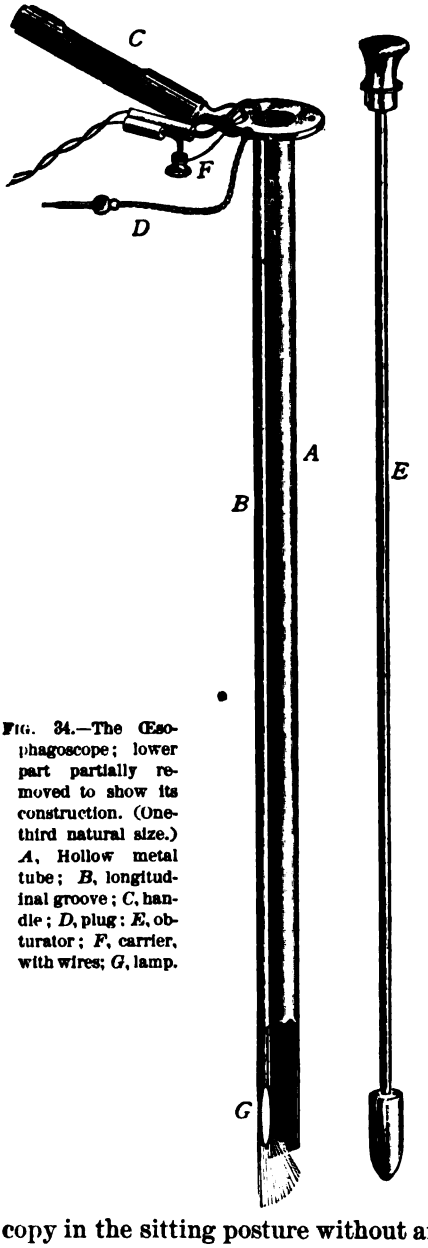

FIG. 34.—The Œsophagoscope; lower part partially removed to show its construction. (One-third natural size.) *A*, Hollow metal tube; *B*, longitudinal groove; *C*, handle; *D*, plug; *E*, obturator; *F*, carrier, with wires; *G*, lamp.

The œsophagoscope which I use* consists, as the accompanying drawing (Fig. 34) illustrates, of a round, hollow metal tube (*A*), having on one side a small longitudinal groove (*B*), which is separated by a thin wall from the lumen of the tube. Two isolated electric wires attached to a carrier (*F**) run through the groove (*B*). At their end a small lamp (*G*) is attached and placed a little above the opening of the tube (*A*), being, however, not inclosed by the thin metal sheet that covers the wires. To the tube is attached a handle (*C*), a plug (*D*), and an obturator (*E*). Before the instrument is introduced the obturator must be in place, and is held there firmly by means of the plug (*D*). After the introduction of the instrument, this plug is removed and the obturator withdrawn. The wires are connected with an electric battery, and everything is now ready for inspection. The handle (*C*) facilitates the use of the instrument.

I usually practise œsophagoscopy in the sitting posture without any anæsthetic (cocaine spray, etc.). The procedure is not a difficult one, and is done as follows:

* The carrier can be easily removed with the lamp, thus facilitating thorough cleansing and sterilization of the instrument and any necessary renewal of the lamp.

Method.—The patient sits on a chair which has a back. The instrument (with obturator inserted) is immersed in warm water, and, while the tongue is depressed with the left index finger, is held in the right hand like a pen and introduced into the mouth and pharynx of the patient. The latter is now directed to throw his head backward and the instrument is then pushed down into the œsophagus without exerting any force.

The accompanying drawing (Fig. 35) shows the position of the patient after the introduction of the instrument. Attention must be

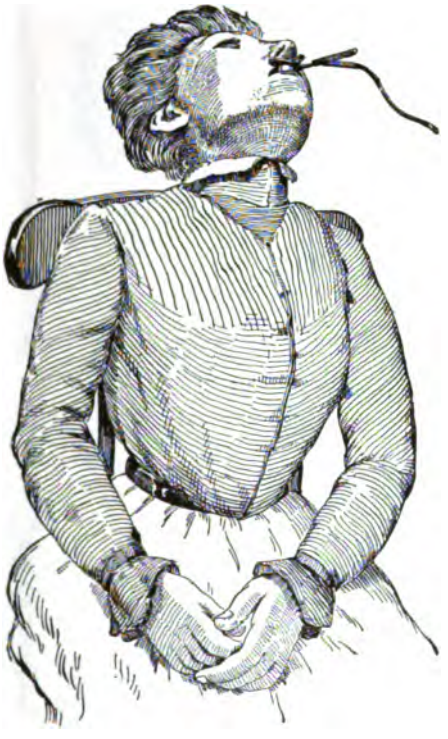

FIG. 35.—Showing Patient with Œsophagoscope Inserted Ready for Inspection.

paid that the lips of the patient are not pressed by the instrument. The obturator is now removed, and the connection made, an inspection may then take place by looking into the tube. At the end of this, the mucous membrane of the œsophagus is plainly visible. If the instrument is slowly withdrawn while looking into it, the whole wall of the œsophagus may thus be inspected.

I have had the œsophagoscope made in two different lengths (35 and 40 cm.) and thicknesses (1 and 1.5 cm.), which will fulfil various indications. The thicker instrument will be used more especially in

the local application of medicaments, or for the removal of foreign bodies, but we can ordinarily get along with the more slender instrument.

The Gastric Douche.

The double-current tube has the disadvantage that its size is quite considerable, and its introduction into the stomach of the patient is not very convenient.

In order to have an apparatus which could be introduced without

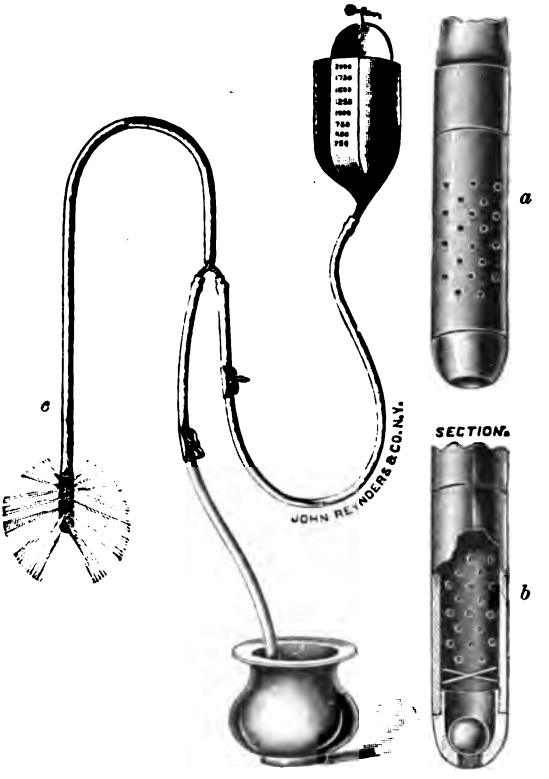

FIG. 36.—The Gastric Douche.

any inconvenience, and which would at the same time allow a thorough douching of the stomach, I have constructed a new gastric douche.[1] Its principle is based upon a valve arrangement. The apparatus consists of a rubber tube, not too flexible (thickness three-eighths of an inch, length twenty-six inches), at the end of which a hard-rubber capsule is attached (Fig. 36, *a*). The latter contains numerous very small openings all around, and one very large opening at its lower extremity. Within the capsule, which can be screwed apart, lies a small aluminum ball. This moves easily and freely within the capsule, and

when it lies above the lower opening it entirely occludes the same. Two cross bars in the capsule prevent the entrance of the small ball into the tube (Fig. 36, *b*). If the tube described is attached to an irrigator provided with a waste pipe, the apparatus is complete. If the waste pipe is closed, and the water made to run through the douche, the liquid will press the ball downward, thus closing up the large opening. The water will then come out through the small side openings like a very fine shower, sprinkling over quite a large area (Fig. 36, *c*). The inflowing tube being closed, and the waste pipe opened while the capsule is inserted into the liquid, the latter will push the ball upward, and thus the large opening will be free, and the water will easily return through it. The liquid will certainly return not only through the large opening, but also through the numerous small side openings. While these, however, do not admit the return of coarse particles, the latter will easily be able to pass through the large hole.

Method.—The douche end of the apparatus is dipped into warm water, and then inserted into the stomach. It is necessary to pay attention that the capsule lies immediately below the cardia, and is not situated deeply in the stomach. The length of tubing from the mouth should be sixteen and one-half to seventeen inches. It may be useful to make a mark at this point of the tube. The tube is now attached to the irrigator, the outflowing pipe closed, the inflowing one opened, and the stomach sprinkled with about a quart of water. In order to make the water return from the stomach, the tube is inserted a little farther into the stomach, about four to six inches, the outflowing pipe opened, and the inflowing one closed. The liquid from within the stomach now returns. This procedure may be repeated three to four times. The temperature of the water should be regulated according to the therapeutic indications. The douche may also be connected with two irrigators, one containing cold, the other warm water; the stomach may thus be sprinkled alternately with cold and warm water.

The Stomach Powder Blower.

By means of the spray only soluble drugs can be applied, but not substances which are either soluble with great difficulty or not at all. In order to facilitate the introduction of the latter I have devised a powder blower for this purpose.[10] The stomach powder blower (Fig. 37) consists of an ordinary, not too flexible rubber tube (*A*), twenty-eight inches and a half long, the distal end of which connects by means of a hard-rubber piece with an air-suction bulb (*B*), the proximate end of which is attached to a hard-rubber piece (*C*). The latter is hollow and pierced with several small openings at the side for the

passage of air, and provided with a screw thread for the capsule. The capsules (*D, E, F*) have numerous holes, and are made in three different sizes (3, 3.5, and 4 cm. long). The capsule of the desired size is filled with the necessary quantity of powder, by means of a small spoon (Fig. 37, *a*), and screwed on to *C*.

Method.—Insufflation of the stomach with powder can naturally be done only when the organ is empty. It should therefore be performed in the fasting condition, and, in cases in which the stomach is not empty in the morning, after previous lavage. Proceed as follows: According to the quantity of medicament required, one of the capsules, *D, E,* or *F,* is filled with the powder and screwed on to the apparatus. The tube is moistened with warm water and inserted into the stomach.

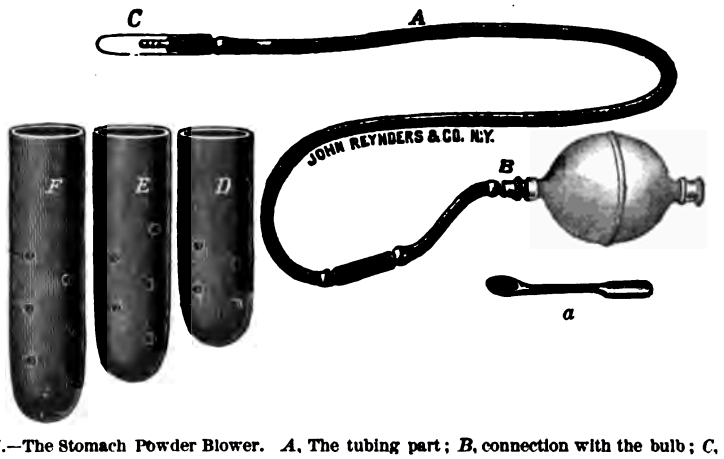

FIG. 37.—The Stomach Powder Blower. *A*, The tubing part; *B*, connection with the bulb; *C*, hard-rubber end with screw-thread for capsule; *D, E, F* (actual size), the capsule-shaped powder receptacles; *a*, the small spoon for putting the powder into the capsule.

The bulb is then compressed three or four times in quick succession. By holding the ear over the gastric region of the patient during insufflation the entrance of air (consequently also of the powder) is distinctly heard. In cases in which there is much mucus in the pharynx and œsophagus its entrance into the holes of the capsule may be prevented by covering them with vaseline in a thin layer. The latter forms a protecting covering and prevents liquids from coming in contact with the powder. When the apparatus is in the stomach and the bulb compressed, the air opens up the vaseline layer over the holes, and the powder can now escape.

The following simple experiment shows that the powder does not collect merely at one spot, but rather spreads over the entire surface of the gastric mucosa:

Take a rubber bag (seven inches long and six inches wide), insert the end of the stomach powder blower filled with powder, and draw

the strings together (Fig. 38, *A*). Then compress the bulb two or three times and remove the insufflator from the bag. If the latter is now opened, the powder is found equally distributed upon the entire inner surface of the bag (Fig. 38, *B*). This shows that the air dis-

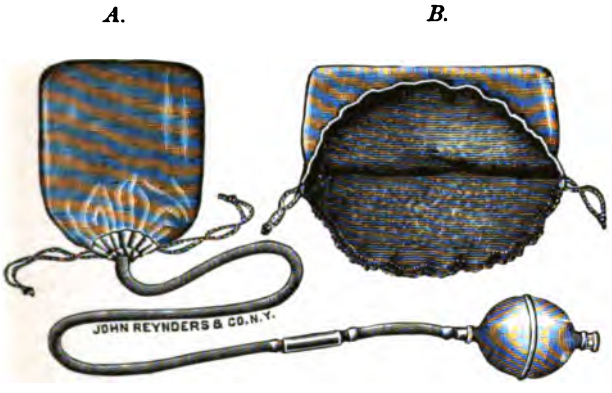

FIG. 38.—*A*, Rubber Bag with the Strings Tightened and within it the End of the Stomach Powder Blower. *B*, The bag opened; the white spots showing the powder.

seminates the powder as fine dust over all parts of the inside of the bag. In the stomach the conditions are not different from those in the bag, and the insufflation of the interior of the gastric cavity with the powder will thus be complete.

I have recently modified this powder blower. The capsule now has three big holes and one small one near the screw thread. Besides, there is a double bulb with a cock arrangement, instead of the single

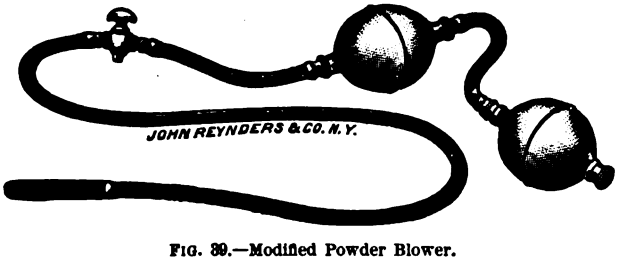

FIG. 39.—Modified Powder Blower.

bulb I formerly used. This modified powder blower (see Fig. 39) acts perfectly, allowing the entire amount of powder within the capsule to be expelled. The capacity of the big capsule is over fifteen grains, *i.e.*, fifteen grains of powder can be thrown into the stomach at once.

The indications for powdering the stomach are manifold: In ulcus ventriculi, bismuth; in gastralgia, orthoform; and in erosion, protargol or suprarenal capsule can be directly insufflated.

Ulcer of the Stomach.

A newly described variety of this disease is the exulceratio simplex (Dieulafoy) or superficial ulceration of the stomach.

It has been observed by several clinicians that extensive hemorrhages (even lethal) from the stomach may occur even when no distinct ulcer can be discovered in this organ. A few such cases with autopsies have been reported. The hemorrhages have been ascribed to parenchymatous bleedings (*Faltenblutungen*). Very small ulcerations causing fatal hæmatemesis have been observed by Chiari[11] and Murchison.[12] Chiari described a case of fatal bleeding from the stomach resulting from the erosion of a submucous vein within an abrasion of the mucous membrane, only the size of a large barley corn. Murchison reported two cases of fatal hæmatemesis from minute ulcers perforating a small artery in the coats of the stomach. He says: "They are remarkable not only for the minuteness of the ulcers which are little more than hemorrhagic erosions, but also for the absence of the usual symptoms of ulceration of the stomach. Neither of the patients had suffered from vomiting prior to the occurrence of the hemorrhage."

Dieulafoy[13] has minutely described a considerable number of similar cases of this affection under the heading "Exulceratio Simplex." This brilliant clinician gave a most vivid picture of the affection in question, which in the main we will make use of for our text. The term, "superficial ulceration" well characterizes the disease under consideration and may therefore be used with advantage.

Steven[14] likewise described two cases of severe gastric hemorrhage due to a very superficial abrasion of the gastric mucosa. In the middle of the affected area there were two pinhole openings through which a bristle could be passed directly into one of the primary lateral branches of the gastric artery.

Definition.—A superficial, usually round, sometimes elliptical, loss of substance within the stomach, involving merely the mucous membrane and also slightly the muscularis mucosæ and usually some small blood-vessel, but not penetrating deeper into the other coats of the organ, causing extensive hemorrhages.

Morbid Anatomy.—The exulceratio simplex consists of an oval superficial defect of the gastric mucosa, varying in size from a five-cent to a fifty-cent piece. The defect involves merely the gastric mucosa and also the muscularis mucosæ, but not the submucous or the other tunics of the stomach. The margins of this defect are not indurated and consist of almost normal tissue. In the middle of the defect very often a minute open blood-vessel is noticeable. Macroscopically the exulceration can be discovered at the autopsy or at an

operation only after a thorough search, the defect being so small that it easily escapes notice. Sometimes the ulceration may be situated under a fold of the gastric mucous membrane, and for this reason the rugæ must be thoroughly examined. Occasionally the affected area is surrounded by a somewhat reddened ecchymotic zone. The microscopical examination shows that the defect is due to a disappearance of the gastric mucosa with its underlying muscularis. The mucous membrane of the stomach is otherwise healthy throughout. The exulceratio simplex has no place of predilection and may be situated anywhere within the stomach.

The *etiology* of this affection is not yet known. Most probably the exulceratio simplex represents an acute and beginning stage of the ordinary ulcer of Cruveilhier. Whether a toxic element is the fundamental cause is still uncertain. The affection occurs principally in persons of twenty-five to thirty years of age.

Symptomatology.—The disease begins with severe large gastric hemorrhages which recur at short intervals. In the midst of health the patient is suddenly overcome with vomiting of very large quantities of blood (half a litre to one litre), which may be also accompanied by melæna. Within a few days after the onset of the disease, sometimes even within a few hours, the patient may be moribund. He resembles a man in whom an artery has been opened and who dies from the hemorrhage. There is almost always, following the hemorrhage, a rise of temperature which is of irregular type and lasts a few days. The general symptoms are not very different from those encountered after any considerable loss of blood and consist in phenomena of extreme anæmia of the brain, dizziness, light-headedness, tinnitus aurium, syncope. The disease very often ends fatally as a result of the exsanguination. In some of the cases, however, the hemorrhage after having occurred two or three times does not reappear and the patient gradually recovers.

Diagnosis.—A probable diagnosis of exulceratio simplex can be made if there have been no gastric symptoms whatever previous to the present disease, and extensive hemorrhages from the stomach recur at short intervals. In exceptional cases there may have also been present gastric symptoms, like gastralgia, nausea, vomiting. Most frequently, however, the hemorrhage appears in the midst of perfect health. The differential diagnosis between ulcer of the stomach and exulceratio simplex is certainly very difficult and can hardly ever be made without a necropsy or an autopsy *in vivo*. In the ordinary ulcer, however, there are always preceding pains and other gastric symptoms, and the hemorrhages are as a rule not so large. In erosions of the stomach the disease shows a chronic type and there are no profuse hemorrhages.

The *prognosis* of exulceratio simplex is extremely grave.

Treatment.—The treatment of superficial ulceration of the stomach coincides with that of gastric hemorrhage. The patient should be kept abed, perfectly quiet with an ice bag over the gastric region, should not be allowed to take anything by the mouth, and be nourished by the rectum. Subcutaneous injections of decinormal salt solution should be frequently made. Dieulafoy recommends subcutaneous injections of 200–500 gm. at a time of the following solution:

℞ Sodium chloride, ...	8.0
Caffeine benzoate, ...	0.1
Water, ...	1,000.0

Oxygen inhalations and injections of ether and camphor must be frequently made when attacks of syncope are imminent. In order to favor the arrest of the hemorrhage by means of coagulation, subcutaneous injections of a two-per-cent. gelatin solution in the amount of 100 gm. at a time can be employed with great advantage. I have used this procedure in two cases of very severe gastric hemorrhages, one due to an ordinary ulcer, the other most probably due to a superficial ulceration, with good result. It is self-understood that thorough sterilization of the gelatin solution and perfect asepsis in the manipulation of the injections are required. The injections are best made in the gluteal region.

In cases of a very severe type, Dieulafoy recommends operative intervention. The stomach is opened and the superficial ulceration when found sutured. The indication for surgical intervention exists if the medical treatment proves ineffective, if a copious hæmatemesis appears at short intervals, and syncope becomes imminent.

Cancer of the Stomach.

In establishing the diagnosis of tumor or neoplasm of the stomach, it is necessary to have in mind also the existence of "apparent tumors" of the abdomen,[1] which may be mistaken for real growths.

The apparent tumors which I speak of here relate to swellings found either directly in the epigastrium or the left or right hypochondrium, and have nothing to do with a neoplasm of whatever kind. In most cases of this kind a resistance may be detected by palpation, sometimes even by inspection, lying between the ensiform process and the umbilicus, presenting a rather smooth surface and frequently pulsating. The size of these tumefactions varies between that of a hen's egg and a man's fist. Light percussion always elicits a dull sound over the area of resistance. These apparent tumors are not exactly of frequent occurrence. They may be produced (1) by a prolapse of the left lobe of the liver; (2) by exposure and thickening of the abdominal

aorta; (3) by a hypertrophic condition of parts of the abdominal muscles; (4) by adhesions (?) around the small curvature of the stomach.

The left lobe of the liver may be the cause of the apparent tumor when it is situated in the median line directly under the ensiform process. Frequently we will get above the resistance, especially at the ensiform process, instead of liver dulness, a more tympanitic sound on percussion. The swelling in these cases is of considerable dimensions (size of a fist).

If the apparent tumor is caused by the aorta, it usually lies deep in the abdominal cavity, close to the spinal column, has an elongated shape, and pulsates strongly. The area of resistance is usually one to two thumbs in width and about two inches in length. Such a tumor is often mistaken for an aneurysm.

The abdominal muscles are probably the cause of the tumor if it lies superficially and can be palpated to one side, either right or left, of the linea alba. The resistance usually runs horizontally and measures about one to one and a half inches in breadth by two to three inches in length; its surface is not globular like in tumors caused by the liver, but more flat, although it may be slightly rounded at the sides.

Adhesion of the stomach is hard to determine with certainty. The resistance felt is rather insignificant, small, lying generally in the smaller curvature of the stomach toward the pylorus, and does not show the characteristic distinctions of the three other groups. Whether the tumor belongs to one or other of the four groups is of less importance than the decision of the question whether in a given case we have to deal with a real tumor (neoplasm) or only with an apparent tumor.

In apparent tumors the swelling presents a more or less smooth surface; at all events there are no distinct nodules. The tumor is not always felt with the same degree of distinctness and sometimes may escape palpation altogether. The tumor occupies the position described above, and a high degree of enteroptosis is usually associated with it. As further aids to diagnosis we have the course of the disease, which usually extends over years; the age (it may occur from the time of adolescence to old age), and the malnutrition, which generally is not of recent date but has lasted for a long time.

Achylia Gastrica Simulating Hyperchlorhydria.

I have described [16] cases of achylia which as regards their subjective symptoms are almost typical of hyperchlorhydria. In the latter disease the disturbances (pains, distress, feeling of fulness, etc.) ap-

pearing usually one or two hours after meals, are caused by too great acidity of the gastric contents. At first sight it seems rather strange that we should encounter the same symptoms in cases of achylia gastrica, *i.e.*, when there is practically no gastric juice and hence no acid present. Still this is so, as can be frequently observed.

In these cases the burning sensation and other symptoms (pains, distress, etc.) found in hyperchlorhydria are certainly not due to irritation of the gastric mucosa by acid substances, for these are entirely absent. It may be that the coarser particles of food, especially after the escape of fluids from the stomach, which occurs in achylia at an early period after meals, excite the mucous membrane mechanically in an intense manner by rubbing against it, and this may be felt as burning or pain. That the ingestion of water would ease this sensation is quite evident. The added fluid mingles with the solid particles lying in the stomach and thus lessens the mechanical irritation. But why the addition of food (even solid substances) should give relief to the pain and burning in some of these cases requires further explanation. It may be that the act of eating, as such, fully occupying the mind, draws the attention away from the stomach and therefore the pain or discomfort is allayed (in reality forgotten).

Cases of achylia gastrica presenting subjective symptoms almost identical with hyperchlorhydria are not very rare. I have observed six cases of this type during one year.

The diagnosis in these cases must be made after repeated examinations of the gastric contents, which show the characteristic features of achylia gastrica.

The prognosis of this special variety of achylia is not different from that of other forms of achylia gastrica and is good, unless grave complications especially of the intestine develop. As a general rule, improvement is observed. As a matter of fact, all my patients during this year were benefited by appropriate treatment to such a degree that they finally presented almost no subjective symptoms whatever.

Besides the usual treatment of achylia, the cases described require special attention for their hyperchlorhydric symptoms. The use of water (half a glassful or a glassful) about one or two hours after meals, just at the time the distress is experienced, appears to be very rational. The water acts as a diluent and diminishes the rubbing of solid particles against the gastric walls (as already mentioned above). Experience teaches that in many of these cases this simple means brings relief. In a few instances milk and crackers were given between meals also with benefit. If these measures are not sufficient, the bromides will then be found useful, bromide of sodium or strontium being given in twelve-grain doses twice daily.

Dyspeptic Asthma.

Asthma due to digestive disturbances was first described by Henoch [17] under the name of asthma dyspepticum. The original communication of this clinician referred to the occurrence of the condition during acute digestive disturbances in children. His patients all had alarming symptoms—the dyspnœa being of a high degree and attended with cyanosis and cold extremities—and failed to improve under the ordinary stimulants, but entirely recovered after a treatment directed against the disturbances of the digestive tract.

Silbermann,[18] Barié,[19] Lauterbach,[20] Oppler,[21] Boas,[22] Ehrlich,[23] Murdoch,[24] and myself [25] have written on this subject.

Cases of dyspeptic asthma can conveniently be classed into two main groups: 1, cases in which dyspeptic asthma appears in an acute form, periodically; 2, cases in which dyspeptic asthma assumes a more chronic type.

The first group is characterized by the occurrence of attacks of asthma at more or less prolonged intervals, either without an apparent preceding cause or after distinct excesses in eating, drinking, or smoking or undue excitement. The attack is usually of a very severe type, often assuming alarming symptoms—extreme dyspnœa, cyanosis, almost collapse.

The second group, that of chronic dyspeptic asthma, embraces the larger number of cases, and may again be divided into two separate categories: (*a*) cases in which the attacks of asthma appear quite soon after meals, either without any particular provocation or after some slight exertion; (*b*) cases in which the attacks usually occur two or three hours after meals, either spontaneously or again after some exertion—walking, etc. In a certain number of the latter category the attacks can be checked by partaking of a small amount of food.

Cases belonging to category (*a*), of group 2, resembl every much true angina pectoris, which is so often encountered in arteriosclerosis of the coronary arteries. Their differentiation from the latter is often very difficult. For even in true angina pectoris, at the beginning there will be attacks without any discoverable lesions of the heart or blood-vessels. Such cases may for a long time appear as dyspeptic asthma until all of a sudden there are distinct signs indicating the heart involvement, as, for instance, a sudden appearance of albumin in the urine or irregularity of the pulse, etc.

The differentiation between dyspeptic asthma belonging to this category and true angina pectoris is not always easy. As a rule, however, cases of dyspeptic asthma are amenable to treatment; that means that a rational régime with regard to the digestive apparatus is followed by good results. These cases also are often capable of a per-

manent cure. Cases of angina pectoris caused by cardiac lesions are, however, much less amenable to treatment, and if improved, the amelioration is only transient.

A great many of my cases of dyspeptic asthma have been examined with regard to the secretory condition of the stomach. Although no constant anomalies were found, it is noteworthy that a considerable number of the patients suffered from achylia gastrica; hyperchlorhydria likewise was often encountered. In both these conditions a rational treatment of the gastric affection was frequently crowned with favorable results so far as the disappearance of asthma was concerned. The explanation why two such contrary conditions may produce the same phenomenon may be found in the fact that in both probably an undue irritation of the gastric mucosa takes place. In hyperchlorhydria it is the hyperacid gastric juice, in achylia the mechanically unchanged coarse particles of food, which irritate the mucous membrane of the stomach and thus reflexly the vagus fibres.

In those cases in which the gastric secretion is more or less normal it will be necessary to assume a condition of hyperæsthesia of the stomach in order to explain the cause of the asthma. This was already done by Boas.

Floating liver was noted in a considerable number (five) of these cases. There is hardly any doubt in my mind but that the abnormal position of the liver, dragging the diaphragm downward, is the cause of the existing dyspeptic asthma in these cases.

The treatment must be directed first toward relieving any existing disorders of the digestive tract; second, toward correcting any abnormal position of the abdominal organs, principally the liver. A regular mode of life, avoidance of too much tobacco and alcoholic drinks, also of too much mental worry and strain is always of importance. By paying attention to these points the majority of cases of dyspeptic asthma will not only be temporarily relieved, but often radically cured.

Syphilis of the Stomach.

Dyspeptic symptoms not infrequently occur in the secondary and tertiary stages of syphilis. While in the secondary stage, however, the digestive disturbances are attributable to the constitutional condition, to the fever, etc., and hence are to be regarded as concomitant phenomena of the original disease, without any special involvement of the stomach, the affections of the stomach in the tertiary stage of syphilis are of independent nature, caused by anatomical processes in that organ.

The lesions of the stomach during the tertiary stage of syphilis may assume various forms (erosions, ulcers, tumors, stenosis of the pylorus,

gastralgia, etc.), all of which present the features of the ordinary types of these affections; their syphilitic nature cannot be recognized by the symptoms alone. Diagnosis of their syphilitic origin is facilitated, first, by the demonstration of a previously existing luetic infection; secondly, by the presence of syphilitic manifestations in other portions the body; and thirdly, by the successful results of antisyphilitic treatment.

It is scarcely necessary to mention that syphilitic subjects may suffer from any of the diseases of the digestive tract without there being any connection between the latter and antecedent lues. Indeed, these cases probably constitute the majority. Hence it is the more difficult to decide in any given case whether the disease of the stomach is of a syphilitic nature or not. Yet this is quite often possible.

Syphilis of the stomach has been observed by Andral,[26] Wagner,[27] Lancereaux,[28] Cornil,[29] Chiari,[30],[31] Stolper,[32] Gaillard,[33] Mracèk,[34] Osler,[35] Hemmeter,[36] Dieulafoy,[37] Fournier,[38] Flexner,[39] Mackay,[40] Fraenkel,[41] Aristoff,[42] and myself.[43]

The cases which I have observed may be differentiated into three groups namely: I. Gastric ulcer of syphilitic origin. II. Syphilitic tumor of the stomach. III. Syphilitic stenosis of the pylorus.

Group I. (syphilitic ulcer of the stomach) is chiefly represented clinically in the literature. I have observed two cases belonging to this class. In the first case (Mrs. A. K.) other signs of tertiary syphilis existed, while in Case II. (Carrie W.), aside from the lesion of the stomach, nothing further of luetic nature could be found. In both cases the customary methods of treatment of gastric ulcer were entirely or partially unsuccessful, while antisyphilitic therapy was followed by complete recovery.

The second group (syphilitic tumors of the stomach) has received but scant mention in the literature, as far as I have been able to learn, except in a few reports of autopsies, and has not been described as having been recognized during the lifetime of the patient. I have described two cases belonging to this group and they are therefore the more significant. The occurrence of syphilitic tumors of the stomach is quite rare, but none the less important. They may run their course in a similar manner as carcinoma, and readily be mistaken for the latter. On palpation such a gummatous tumor may evince all the characteristics of a malignant neoplasm, and even the symptoms may so strongly resemble those of cancer as to be confounded with the latter.

It would appear therefore advisable in every case of neoplasm of the stomach to bear in mind the possibility of syphilis, and to question the patient as to any previous history of that disease, and examine for any other syphilitic manifestations on the body.

The third group (syphilitic pyloric stenosis) is of great practical

import. In one of the cases I have observed a thickened pylorus could be felt as an oval tumor which disappeared under continued antisyphilitic treatment. At the same time the symptoms of ischochymia receded, and the patient recovered. In a second case the pylorus was not palpable, and the diagnosis of the commencing constriction had to be based upon the results of internal examination of the stomach. In both cases the customary medical measures indicated in benign pyloric stenosis proved insufficient, while the administration of potassium iodide soon effected the improvement.

From the remarks just made it appears distinctly that tertiary syphilis may produce severe gastric affections which are amenable to antiluetic treatment. In the therapeutics of intractable diseases of the digestive apparatus, therefore, the possibility of a syphilitic origin of the trouble must never be forgotten.

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DISEASES OF THE LIVER.

BY

CARLO GIOFFREDI,

NAPLES.

Physiology.

Glycogenesis.—From the time of C. Bernard's discovery to the present day, an uninterrupted series of physiological researches has been directed to a demonstration of the conditions of the glycogenic function, the formative substances of hepatic glycogen, and the causes and conditions of the transformation of glycogen into glucose. To Bernard also we owe a knowledge of the fact that the parenchyma of the liver is richly or poorly supplied with sugar according to whether the death of the individual occurs rapidly or slowly. After the researches of Colrat, Fochier, and Colomb had been made, Lacassagne and Martin suggested the application of the glycogenic function of the liver to forensic medicine, holding that the presence, especially the abundant presence, of sugar in that organ indicated rapid death in the newly born infant as well as in the adult; while the absence of glucose would go to prove a slow death.

The conclusions of Lacassagne and Martin have, however, not been confirmed by other experimenters. Modica, in fact, reaches entirely different conclusions. In patients who die from ordinary diseases, whether these be of long or of short duration, the liver is not apt to lose its entire supply of glycogen or of glucose, which may be found in that organ several hours after death. The glycogen does not long remain as such in the cadaver, but it is not accurate to state, as is generally done, that it is rapidly transformed into glucose. Moreover, as the amount of glucose in the liver after death represents the glycogen which was already present in that organ, and depends therefore upon the changes to which the liver was subjected, it is evident that the presence or the absence of the glucose cannot be of decisive differential value, as to whether death was due to traumatic or to pathological lesions. Lacassagne and Martin's theory considered by itself cannot be of special value in forensic medicine, since it may lead to the gravest errors.

Following the modern pharmacological methods, which consist in studying the pharmacodynamic action of medical substances on the various organs and cellular tissues, Cavazzani has investigated the action of certain drugs on hepatic glycogenesis, thus making an important contribution to the rational therapy of diabetes of hepatic origin. He has given especial attention to the action of curare, of atropine, and of methyl violet on the thermogenesis and the glycogenesis of the liver, and from the result of his numerous experiments he has come to the conclusion that all three prevent or reduce to a minimum the increase of temperature observed in the livers of those who die from asphyxia, and that they also interfere with the production of glucose. Methyl violet is capable of entirely preventing the post-mortem transformation of glycogen into glucose.

These experimental researches point out a new field for rational therapeutics, and one from which we are warranted in expecting great things in the treatment of glycosuria of hepatic origin.

Action of the Liver on Uric Acid.—In our previous article we discussed at length the relations between the hepatic functions and uricæmia, and reached the conclusion that the liver has no influence on the condition; moreover we held that a study of the clinical and experimental data shows that the involvement of the liver in gout is the result and not the cause of the accumulation of uric acid in the blood, —the liver being forced to hyperactivity for the destruction of the excess of uric acid, probably transforming it into more highly oxidized products of combustion. The recent researches of Ascoli give the experimental proof of our clinical deductions. From his experiments it may be concluded that the disappearance of the uric acid is to be attributed to the physiological activity of the hepatic cell, and that the liver is capable of destroying an excess of uric acid which may be found in the blood. So that what we held theoretically has now been proved, namely, that the liver can destroy or transform uric acid, and that the involvement of the liver in gout is the result and not the cause of uricæmia

Another corollary belongs to this observation. When, as in gout, in infective processes, and in leukæmia, the amount of uric acid eliminated in the urine is taken as an estimate of the amount of nuclein which has taken part in metabolism, or of the amount of uric acid formed, we should take into account the destructive action of the liver on uric acid. The value of such conclusions must, however, be limited, so long as the proportions and the conditions regarding the destructive element are so imperfectly understood.

It would be of great importance to ascertain the compounds into which the uric acid is transformed, and whether the liver changes it into urea—which would do much to clear the pathogenesis of gout.

In any case it may be asserted that the hepatic function is of great importance in pathological abnormalities of metabolism, especially in regard to nuclein.

Protective Action.—The protective function of the liver has offered great attractions to investigators, who are desirous of ascertaining whether it is exercised in regard to poisons of a different nature from the vegetable alkaloids and the mineral poisons over which it is known to have an influence.

Tedeschi made a series of researches with ricinin, a toxalbumin found in the seeds of the castor oil plant, to ascertain whether the action of the hepatic cells could compensate or overcome its toxic properties. His experiments, directed to a determination of the minimum lethal dose of the poison, show that the effect is most marked when it is administered hypodermically, next through the endovenous tract, then the portal vein, the peritoneal tract, the intestinal and finally the gastric tract. In another series of experiments he endeavored to modify the functions of the hepatic cells either by injections of antipyrin and sugar (Dufourt, Lépine), or of glycerin (Ewald), and to alter the intestinal functions by heat at 70° or by the injection of fluoride of sodium, and then to ascertain the action of ricinin under these different conditions. The results obtained showed that while the toxic effects of the substance were not greatly changed so far as the liver was concerned, they were markedly altered when it was a question of the intestines.

That the liver possesses an antitoxic influence on ricinin cannot be denied, but it is evidently far inferior to that of the intestines, either because the latter makes use of its powerful expulsive properties, or else because it is so rich a field for the culture of bacteria and of ferments, or perhaps because of the activity of its epithelial cells. Researches into the antitoxic power of the liver have not been confined to a study of its actions in the case of poisoning by toxalbumins.

We know from Rummo's studies, especially, that heterogeneous blood serum is toxic (especially if administered endovenously). Now Giussano has demonstrated that a rabbit will tolerate a much larger injection of ox blood through the mesenteric vein than through the jugular vein or the veins of the ear. So that it is evident that the liver extends its protective power even against heterogeneous serum.

Another important line of research has been undertaken, namely, the determination of the hygienic conditions which affect the antitoxic powers of the liver, either increasing or diminishing them. Roger and Garnier, by means of their method of studying the hepatic functions in a rabbit through sulphuretted hydrogen, have seen that the younger the animal the greater the functional activity—in other words, that the amount of sulphuretted hydrogen retained in the liver for a

kilogram of animal is in inverse ratio to the weight. This is, however, under the condition that the animal be well fed, for, as they have shown experimentally, the activity of the hepatic cell varies according to whether the animal has received an abundant and appropriate diet, or a limited one, or is in a state of fasting. From which Roger and Garnier argue that the natural stimulus of the hepatic cell is to be found in the food, fasting or an insufficient diet diminishing the protective action of the liver against sulphuretted hydrogen. And as it was already known that these conditions interfere with glycogenesis, the researches of Roger and Garnier are an additional proof of the relation existing between the action of the liver on poisons and its action on sulphuretted hydrogen.

All these experiments go to prove the protective function of the liver not only in respect to organic and inorganic poisons, but also in regard to toxalbumins, and the conditions liable to influence this important action of the hepatic cells are under investigation.

Modern researches have also been directed to the best methods of utilizing the protective power of the liver clinically, and the experiments of Roger and Garnier are an attempt in that direction not to be overlooked. They propose that suphuretted hydrogen shall be the indicator of the protective action of the liver. A certain amount of the substance is introduced into the intestines, and the amount given out in the expired air is estimated by means of acetate of lead paper. This method is founded on the fact that five times more of the gas must be introduced into the portal vein than into the peripheral veins to obtain the characteristic reaction on the paper. The liver therefore must take up a notable amount of the sulphuretted hydrogen; on the other hand, to disturb the hepatic cell in its functions, as in experimental phosphoric intoxication, the necessary dose is only half as much, and the animal will show but little sign of disturbance.

In rabbits 4 to 5 c.c. of phosphorus, which is a specific poison to the hepatic cells, introduced by the rectum was sufficient to give the characteristic reaction in the expired air.

This method, however, although of easy application experimentally, is not very available clinically, because, as even Roger and Garnier admit, in man we never have sulphuretted hydrogen in the expired air, no matter how large the dose introduced into the rectum. It is therefore purely of laboratory interest, and can serve no purpose in the diagnosis of the functional condition of the liver.

Chauffard and Castaigne have proposed another method for demonstrating functional activity of the liver. They hold that the intermittent elimination of methylene blue which has been injected subcutaneously, very perfectly reveals insufficiency of the hepatic cell. In healthy individuals they have found the elimination to be continuous,

cyclic and polycyclic, but never intermittent, while in persons suffering from liver troubles the curve of elimination was always intermittent. In patients with nephritis, on the other hand, the methylene blue was always tardy in making its appearance in the urine, and its elimination, which in two cases was intermittent, was delayed; in one of these cases, however, there was every sign of hepatic insufficiency (alimentary glycosuria, hypoazoturia, urobilinuria).

These clinical results are as yet too incomplete to be accepted as in any way decisive, especially because the facility with which renal disorders occur in sufferers from hepatic troubles might lead to the conclusion that the disturbance in the elimination of methylene blue is due to a lesion of the kidneys rather than to disease of the liver.

Hæmatopoietic Functions.—As to the part played by the liver in sanguinification, Popelski has instituted researches on dogs, producing direct emission from the vena porta to the vena cava by means of Eck's fistula. He was unable to establish any marked modification in the erythrocytes, or in the amount of hæmoglobin, but the leucocytes showed variations worthy of note. After the operation there was at first a great increase in the number of young leucocytes, while the adult leucocytes were diminished; later the opposite condition prevailed, with a great increase of the adult leucocytes. The blood passing through the liver left there the greater part of its adult white corpuscles. Verigo and other writers have found in the liver many white corpuscles containing bacteria, which is a confirmation of the results obtained by Popelski. The young leucocytes, on the other hand, which are more capable of keeping up the struggle, are not retained by the liver and are poured into the circulation.

Still more recently Gioffredi, in an experimental thesis which has not as yet been published, takes up in a comprehensive manner the subject of the hæmatopoietic function of the liver in various animals (fish, amphibia, mammals). From the result of his numerous experiments on various animals, he concludes that in adult life, and when completely developed, the liver has no hæmatopoietic action, but is, on the contrary, the seat of decomposition of the old blood corpuscles. In embryonal life, however, we must admit the hæmatopoietic function of the liver, and thus accept the theories of Foà, Salvioli, and Bizzozero, already described in our previous article.

In the last few years clinical researches have not been lacking in regard to the morphological and chemical composition of the blood in hepatic disease. Wlaiëff has studied the condition of the blood in healthy adults, and in patients affected with various hepatic disorders. According to this authority, an examination of the blood enables us not only to diagnose hepatic lesions, but also to determine their nature. Hydatid cysts give scarcely any change in the blood, while

cirrhosis causes a diminution in the erythrocytes down to 3,000,000 per cubic millimetre, and an increase in the white cells, not, however, beyond 20,000 to the cubic millimetre. Hæmoglobin is diminished one-half. There is also diminution of the lymphocytes with increase of the polynucleated leucocytes.

In malignant tumors of the liver the number of the white cells varies from fifty to sixty thousand, and that of the red cells sometimes is lowered to less than a million. Of the leucocytes about ninety-three per cent. are polynucleated, even the red corpuscles are nucleated, and we may find poikilocytosis. There is a notable difference between these conditions and those found in other anæmic states, as, for instance, in pernicious anæmia, in which the leucocytes are diminished *in toto*, without alteration of form, or pseudoleukæmia, in which the ratio of the various leucocytes is normal, etc. From his studies Wlaiëff concludes that the hepatic cells assisted by the lowered pressure in the portal system take the noxious principles from the blood, and restore to it the elements necessary to its life and functions.

This condition of things is, however, changed in hepatic disease; the noxious principles are not eliminated, but cut short the life of the red blood cells, and interfere with the successive changes undergone by the white cells.

Wlaiëff's researches as thus interpreted may be confirmed by the point of view taken of the functional activity of the liver. We must not, however, conclude that the liver is in reality a hæmatopoietic gland. The grave alterations in the red cells found in advanced stages of liver disease, especially in tumors of the liver, may be a result of the cachexia induced in the general system, and do not therefore differ from those observed in other forms of dyscrasia. Neither does it seem to us that the special morphological changes in the blood constitute a point of diagnosis of any importance in hepatic diseases, because hæmatology has not yet reached the stage of recognizing special alterations for the different forms of cachexia.

General Pathology.

Hepatic and Nervous Disorders.

The interesting advances made in the physiology and pathology of the liver, as well as the views now generally accepted in regard to autointoxications, have changed the theories formerly held of the relation between diseases of the liver and those of the nervous system, which were based on the old idea of humoral medicine, and have claimed the attention of clinicians as well as investigators. And as the liver by degrees assumed greater importance in their eyes the more

they studied its complex functions, a new method of research was initiated, whose object was to discover what disorders of the central and peripheral nervous system could result from hepatic disease—in other words, whether true forms of neuropathy could be of hepatic origin.

We must, in the first place, bear in mind that some of the nervous phenomena occurring during the course of a liver disease may be simply a coincidence. Neuralgia in a person affected with liver trouble, cerebral hemorrhage occurring in a cirrhotic patient, delirium in an alcoholic affected with interstitial sclerosis may not indicate the slightest connection between the nervous disorders and the liver. In many cases both classes of symptoms may be due to one and the same cause, as, for instance, alcoholism or chronic lead poisoning, without being otherwise connected.

Neither should the nervous symptoms which occur toward the close of hepatic disease be considered of hepatic origin, as they may be due to the inanition from which such patients suffer, a condition which it is well known may profoundly affect the functions and even the structure of the cerebrospinal axis. The nervous disorders may be the result of some intercurrent infection, such infection being likely to occur because of the deficient functional powers of the liver.

In order that nervous symptoms should be unmistakably of hepatic origin, there must be definite symptoms of hepatic lesion, without the involvement of any other organ to which the nervous disorders could reasonably be attributed.

Nervous troubles due to liver disease may be observed in the course of widely differing affections (cirrhosis, fatty degeneration, cancer), and the most important ones are seen at the terminal period of the malady. They take the chief rôle in the course of acute yellow atrophy, whether primary or secondary.

Levy divides the nervous phenomena of hepatic disorders into two classes, the slight and the grave. The former may be motor, sensory, of the special senses, or mental.

(*a*) Motor symptoms. Muscular asthenia is frequent in the course of liver affections. It may consist merely of a general weakness, or may reach such a degree that the patient can scarcely move himself in the bed. This asthenia may be of exclusively nervous origin, but in some cases it must be attributed to the deficient glycopoietic functions, or to the accumulation of lactic acid in the muscles.

(*b*) Sensory symptoms. These are nearly always purely subjective, and consist in headaches which are often frontal, general pruritus which cannot be accounted for, and a sense of general lassitude. In a few rare cases (Hayem, Gouget) the motor and sensory disturbances are associated, and present the form of a peripheral neuritis

(weakness of the upper or lower extremities, with pain, both spontaneous and exaggerated on pressure).

(*c*) Symptoms of disorders of special sense. These are limited to the visual troubles so well described by Vincent Baas, and Scabrook. Hemeralopia, characterized by an abnormal diminution in the acuteness of vision, especially in insufficient light, is not rare in cirrhosis. It usually occurs late in the disease, but may appear early, and varies greatly in severity without appreciable cause; it has been supposed to be due to a modification of the secretion of the retinal purple, or to œdema of the retina. Other important lesions of the eyes have been found in the course of liver diseases, as amblyopia, amaurosis, asthenopia, iritis, and color blindness (Scabrook).

(*d*) Mental symptoms. Insomnia or somnolence may occur. The former is rare, and has not the significance of the latter which is often the precursor of more grave nervous conditions. Murchison observed somnolence at an advanced period of cirrhosis, and it may be so marked as to deserve the name of narcolepsy.

A change in the disposition of hepatic patients is frequently noticed, characterized by restlessness, irritability, indifference, apathy, and even absolute melancholy.

Grave nervous phenomena sometimes but rarely appear temporarily during the course of an hepatic affection; they are more likely to be terminal and ante-mortem symptoms, and consist in excitement or depression, the one frequently following the other. Convulsions have been noted by Graves and Teissier in cirrhosis. They are usually limited to certain sets of muscles and occur in the form of cramps, but in rare cases they may be general, and have been observed in alcoholic patients and in children.

Certain cases of eclampsia noted by Whitla in scarlatina, and by Mya in rachitis, are, according to these writers, traceable to hepatic insufficiency. A number of other authorities, especially Pinard, attribute to hepatic insufficiency the chief rôle in the production of slight nervous disorders seen in pregnancy (change in disposition, somnolence, headache, pruritus, ptyalism, vomiting), as well as of puerperal eclampsia. The constant presence and the gravity of the liver lesions found in patients who have died of eclampsia point to the preponderating influence of hepatic insufficiency in the pathogenesis. The question is as yet, however, not wholly solved. Other organs, especially the kidneys, may be affected, and before giving a decided opinion on the matter, the initial cause of all the lesions should be determined.

Other nervous phenomena, such as trismus, trembling, and tetanus, have been reported in hepatic diseases, but further confirmation is needed. Delirium is not rare in the course of liver disease, but is

most likely to occur toward the end. It affects both words and actions, is chiefly nocturnal, subcontinuous, usually calm, characterized by dreams and incoherence, and accompanied by considerable weakening of intelligence and memory. Sometimes the patient tries to get out of bed, loses his knowledge of surrounding objects, searches for things that cannot be found, or tries to get into his neighbor's bed. At the terminal period of primary cancer of the liver and of grave icterus, the patient may become excited and raging, and Fräntzel and Traube consider maniacal attacks to be constant in acute yellow atrophy. But this is not all. According to Klippel, certain forms of alcoholic delirium are the result of an autointoxication, due to the effect of the ethylic poison on the liver. This writer attributes to hepatic insufficiency an important part in the production of insanity, basing his theory on a few cases in which hepatic delirium resembled mental alienation. Joffrey has reported an observation of general paralysis of hepatic origin; Pierret and Teissier attribute great importance to an intoxication of hepatic origin in the production of certain cases of paralysis agitans, exophthalmic goitre, and even of progressive muscular atrophy and of tabes.

Symptoms of depression of the nervous system are, however, the more frequent, and chiefly take the form of coma. In rare cases this is transitory, but as a rule it constitutes the final stage in hepatic insufficiency. It is absolutely exceptional for it to be the diagnostic symptom of an hepatic disease, as in a case of Whitla's. The coma, which is more or less profound, is sometimes accompanied by paralyses or contractures. The conjunctivæ are frequently injected, the pupils dilated, sometimes temporarily unequal, and they react to light very slowly, or may be entirely inert. The patellar reflex is more likely to be normal or abolished than exaggerated. The snoring respiration may take on a special rhythm, consisting in a slow inspiration followed by a brusk expiration and then a long pause. The Cheyne-Stokes respiration may be noted, but it is not absolutely certain that it occurs in hepatic insufficiency without any renal lesion. Asthmatic attacks have been known to precede the coma.

The heart's action is accelerated, perhaps irregular, the pulse small. Finally, the coma may be preceded by vomiting, exceptionally by syncope, or it may be accompanied by hiccough, or retention or incontinence of urine. These grave symptoms of hepatic insufficiency may occur singly or in groups. In the latter case the symptoms of excitement are usually the first to appear, and coma closes the scene. It rarely comes abruptly, but is as a rule preceded by torpor or by subdelirium.

There is an evident analogy between the symptoms obtained experimentally and those accompanying hepatic insufficiency in man.

On the other hand, there is no less marked a resemblance between the experimental symptoms and those of uræmia. In fact, the poisons which accumulate in the system are probably the same in both cases, the difference lying in the fact that in the one case their retention in the blood is due to a lack of the antitoxic influence of the liver, and in the other to deficient elimination by the urine.

It would be most important and desirable to know the nature of the toxic substances which accumulate in the system. Everything seems to indicate that the nervous symptoms are not due to any one substance alone, and that a large number of the poisons inherent in the organism or introduced from without are capable of acting on the nerve centres. Many of them undoubtedly originate in the intestine, and this is shown by the occurrence of nervous symptoms when the blood which comes from the intestines is deflected from its course by engrafting the vena porta into the vena cava, and by the accentuation of these symptoms when under these same conditions a meat diet is taken, while they are diminished by an exclusively milk diet.

In short, the variability of the syndrome of nervous symptoms in hepatic insufficiency should be attributed to the great variety of the poisons, to their more or less rapid accumulation, and to some special hereditary or acquired predisposition on the part of the patient.

All of the foregoing clinical and experimental researches have found an opponent in Massalongo, who notes the rarity of nervous symptoms in pure chronic liver diseases, and the greater frequency of their occurrence, when, as often happens, the kidneys are affected at the same time. As a rule the phenomena of autointoxication cannot make their appearance if the kidneys are in a healthy condition. The ease and promptness with which the kidneys eliminate foreign substances dissolved in the blood plasma is well known. If the kidneys become unequal to their task, either from simple functional deficiency or from some anatomical lesions, the phenomena of autointoxication at once enter on the scene, with more or less frequency and severity according to the predisposition of the individual. Massalonga has observed both clinically and anatomically that in cases of chronic icterus and of atrophic or hypertrophic cirrhosis, the kidneys are practically always the seat of epithelial and even interstitial lesions. And experimentation has demonstrated that the abnormal substances eliminated by the urine during the course of hepatic diseases are toxic for the kidneys. So that according to this authority we should not speak of neuropathies from liver disorders, but of neuropathies from hepatorenal toxæmia.

Massalongo's remarks, directed as they are to the restraining of the too marked tendency that there is to regard all hepatic diseases as the last expression of autointoxication, deserve the utmost considera-

tion; but they cannot, and in fact they do not, abolish the fact that in hepatic diseases we may have a classical nervous syndrome. We must of course not make the mistake of attributing any nervous symptom to hepatic toxæmia until we have been able to exclude all other sources; but to attribute all such symptoms to renal lesions and the consequent uræmia is to abandon all the experimental and clinical results described above. The kidneys very surely are the chief source of compensation in hepatic insufficiency, so that if they too are impaired we have at once grave symptoms of autointoxication, but we must admit that these symptoms can and do appear even when the kidneys are normal, otherwise how could we explain the fact that there are forms of chronic poisoning from the most varied toxic substances, with perfectly healthy kidneys? The animal organism is a complex of organs and functions all directed to the one end of preserving the individual. Suffering in one organ or function means suffering of the whole system, which fact explains the relations existing between diseases of the liver and the nervous function which presides over the whole animal economy.

The Liver and Infections.

The protective action of the liver, which was established by means of many and various researches into the subject of intoxications and infections, has been further investigated of late. The action of the liver under experimental infection has been the especial subject investigated by modern workers.

Roger began by making a comparative study of the effects of inoculation of the anthrax bacillus according to whether it was done by injecting into the aorta, or a peripheral vein, the femoral artery, the central part of the carotid, or a branch of the portal vein. In the first case it reached the systemic circulation directly; in the second it went through the lesser circulation; in the third it passed through the cutaneous, muscular, and osteomedullary network of the limb and then the lesser circulation; then penetrating into the systemic circulation; in the fourth case passing through the cerebral and the lesser circulation it entered the general circulation, and finally in the fifth it passed through the portal and the pulmonary before reaching the systemic circulation. The differences observed in the first four cases are but slight, because although some animals may hold out longer than others they all succumb finally; but the results obtained by injections into the portal vein are quite different. In this case we see that the animal can tolerate much stronger doses than would suffice to kill if injected in other portions of the circulatory system—so much so that certain rabbits survived a dose sixty-four times stronger than one which proved fatal when injected into a peripheral vein.

The liver exercises a decidedly protective action in infection by the staphylococcus aureus, but it is of little importance because it neutralizes only eight lethal doses.

In the case of the streptococcus the results are different—the liver exercises no protective function because this microorganism finds the parenchyma of the liver an excellent culture medium, so that animals into which this bacterium is injected through the portal vein succumb before any others. The lungs, on the other hand, exercise a protective power in regard to the streptococcus just as the liver does in regard to the anthrax bacillus and to the staphylococcus, only its destructive powers are less active, as it neutralizes only one lethal dose.

With the coli bacillus the results are somewhat erratic. The first animals to succumb are those inoculated through the carotid and the vena porta, those which receive the virus through the aorta are the last to die. We must therefore admit that the microbes are destroyed by the organs tributary to the arterial system, and possibly in the walls of the intestine itself the coli bacillus may meet with elements capable of destroying its action. What deserves especial notice is the fact that the liver, far from being destructive to this organism, is an excellent culture field for it. This fact, however opposed it may be to teleological theories, explains the frequency and the gravity of hepatic infections of gastrointestinal origin. The anatomico-pathological lesions found in it when the injections are made into a branch of the portal vein are of great importance. The liver is large and yellowish, and its surface shows white spots which under the microscope are seen to reveal fatty degeneration.

These results are, however, in part contradicted by the researches of Lemaire on general infection by the bacterium coli from endovenous injection. If a coli bacillus succeed in causing general infection, it is a sign that its virulence could not be destroyed by the liver. The protective power of the liver toward the organism is readily overcome by increased virulence on the part of the microbe.

The protective action of the liver is likewise brought into play in overcoming the bacillus of dysenteric enteritis. If very recent cultures are used, the rabbits injected through a peripheral vein will succumb, while those injected through a branch of the portal vein will survive. The liver, therefore, is able to overcome the living bacillus, but not its soluble products.

Finally, the liver acts antagonistically to the oidium albicans.

The action of the liver is seen to be of more potency in regard to certain microbes than in regard to poisons. If a toxic alkaloid be injected into a branch of the portal vein, the animal will die when the dose is twice the usual lethal one. The liver acts with more energy

on microbes, neutralizing sixty-four mortal doses of anthrax bacillus and eight of the staphylococcus.

Various hypotheses have been offered in explanation of this defensive action of the liver against infections. According to Verigo's researches phagocytosis is especially active in the hepatic cells. But how shall we explain the fact that it displays so much energy in destroying the anthrax bacillus and the staphylococcus, but is quite unable to delay streptococcal infection, and has no action at all on the coli bacillus? It is probable that so simple an explanation as phagocytosis will not suffice and that the process is a far more complex one; possibly the biochemical conditions of the hepatic tissue should be taken into account, the tissue acting electively upon certain microorganisms, and remaining quite inert to others.

A series of entirely original experiments have been made by Roger with the view of ascertaining the influence of various hygienic conditions and of certain drugs on the protective function of the liver in infections. For this purpose he studied the effects of fasting, of the association of microbes, of glucose, sodium bicarbonate, ethylic ether, and especially of the staphylococcus.

With fasting the protective action of the liver diminished, but rather slowly. After twenty-four hours of inanition it acted as in the normal state on the anthrax bacillus. After two or three days its bactericidal power was weakened, but had not completely disappeared, as was shown by the fact that injection through the portal system was still less rapidly fatal than through a peripheral vein.

Associated microbes, on the other hand, caused a rapid disappearance of all protective power of the liver. Injection of the soluble products of the bacillus prodigiosus into a branch of the portal vein completely annihilated all destructive power of the hepatic gland toward the staphylococcus, so that animals inoculated with these products through the portal vein died as quickly as those which had been inoculated through a peripheral vein, and more quickly than those which had been infected by a pure culture of the staphylococcus through a peripheral vein. The results of this experimentation throw much light on a fact frequently met with in pathology. It may be that the influence of certain toxins in abolishing the protective power of the liver will to a large extent explain the as yet obscure action of associated microbes.

Glucose injected into the portal vein with microorganisms, or introduced by the stomach, exaggerates the protective power of the liver if given in small doses, while if administered in large doses it diminishes and finally completely destroys it.

Sodium bicarbonate in large doses (5 gm. by injection in a branch of the portal vein, 10 gm. by ingestion) rapidly destroys the protec-

tive action of the liver, and the animals are killed by relatively small doses of the staphylococcus. Experimentation is still under way, and it is very likely that small doses of this substance will be found to behave as do small doses of glucose.

Sulphuric ether also gives varied results according to the dose. Large amounts, especially if given intravenously, will inhibit the protective power of the liver, while small amounts will increase it. Roger was able to ascertain that this is not due to any action of the nervous system, upon which, as we know, ether has a marked influence, but to the direct action of the substance on the hepatic parenchyma. It is very evident that these researches not only serve to explain the physiopathology of the liver, but also form a guide to the therapeutic indications to be followed in order that a rational form of medication may be obtained.

For some time researches have been made with a view of ascertaining how and to what extent the protective power of the liver is exerted when experimental infections are produced by means of the toxins of microorganisms, instead of the microorganisms themselves, and we have in our previous article pointed out the results of Roger's work in regard to the toxins of putrefying muscle, of Charrin in regard to the products of the pyocyanic bacillus, and of Camara-Pestana for that of tetanus. Tessier and Guinard have investigated the action of the liver in regard to the diphtheritic and the pneumobacillary toxins. They reached the unexpected conclusion that it had no protective action whatever toward these substances, and that indeed in experiments conducted on dogs the toxins were more energetic in their action when they went through the liver. The pneumobacillary toxin behaves differently according to the place chosen for its introduction; if it is a peripheral vein, certain symptoms appear immediately, and then after a period of rest the fatal symptoms appear. If the injection is into the portal vein, no effect is visible at first, but in half an hour the toxic symptoms appear and death soon follows. This occurs in the dog, but in rabbits the phenomena are more variable, and in some cases the liver appears to exercise a protective power.

Fadoa has demonstrated that animals injected with typhoid toxin through the portal vein succumb the most quickly of all. He found that the liver exerted a certain amount of protective influence in regard to the diphtheritic toxin, which is in opposition to the experimentation of Teissier and Guinard. But Roger's researches lead to the same conclusion as those of Teissier and Guinard, that is to say, that the liver has not the slightest protective influence against diphtheritic toxin.

The different results obtained in experimentation are doubtless due to the complexity and the variability of the various microbic toxins

used. At all events it is probable that the absence of the protective power in certain cases is due to anatomical alterations of the hepatic cells, caused by the passage of a large amount of the toxin. This view is confirmed by the result of Roger's experimentation with the bacillus of dysenteriform enteritis. The liver arrests and destroys this microbe, if a very recent culture be used; but the results are entirely different if an old culture is employed; and, therefore, it is evident that the toxin produced by the microbe and found in the culture destroys the protective action of the hepatic gland.

The action of microbic toxins on the liver having been investigated, a study was made of the various physiological conditions which were able to modify it in any way.

Teissier and Garnier wished to ascertain the action of physiological feeding and of fasting on the hepatic lesions of bacterial toxins. Dogs appeared to offer greater resistance when fasting or on a low diet. At the autopsy the liver of these animals showed lesions less severe than those of animals kept on a full diet. A microscopic examination of the liver of dogs kept on a normal diet and poisoned with the toxin of the pneumobacillus, or of the bacillus of diphtheria, showed marked symptoms of congestion with vascular dilatation, active inflammation in the connective-tissue spaces, accompanied by lesions of the parenchyma and profound cellular alterations; the substance of the lobules was displaced and necrotic, the cells were uneven and deprived of their nuclei, viscid, and sometimes the seat of a granulofatty degeneration. On the other hand, in dogs intoxicated after a prolonged fast, the hepatic lesions were much less severe, and often consisted merely in the following changes: the hepatic tissue generally had a normal appearance; around the blood-vessels there was a marked development of the connective tissue, which was in distinct bundles, without new cells in the fibrillary network, showing that it was non-inflammatory adult tissue. The protoplasm of the cells was, however, of a bad color, and in some places there was true cloudy swelling.

These experimental results, which at first sight appear to be far from what we should expect, knowing as we do that the protective power of the liver is diminished by fasting, become clear if we recall the detrimental action of the toxins on the hepatic parenchyma, and the continuous functional activity of the liver during digestion, the two coöperating to cause the gravest lesions found in the animals kept on a normal diet. The toxic substances derived from the intestinal chemism act as morbific agents on the hepatic cell, which is attacked by microbic poisons.

An important conclusion for the rational therapy of infections and diseases of the liver may be drawn from these researches, and that is that the restricted diet, especially the milk diet prescribed by Sem-

mola, is fully justified, since by reducing to a minimum the processes of intestinal chemism and the production of irritating chemical products, it puts the liver into a condition of rest most necessary to it in order that it may act upon the microbic poisons.

While so many important researches have been made in regard to the condition of the liver in experimental infections, important clinical and anatomicopathological studies have not been lacking for the ascertaining of its lesions in acute infections, and the chief of these have been done by Roger and Garnier.

The researches of Roger and Garnier have been exhaustive, and have been directed to a study of the macroscopic and microscopic characters, and to the chemical composition of the organ. The last-named method of research is apt to be neglected, and yet it possesses the advantage of enabling us to know the composition of the gland, and of permitting an exact appreciation of the quantity of the various substances which enter into its composition, and of the changes which they may undergo.

According to the results obtained by these investigators, the liver in scarlet fever is increased in size, pale in color, sometimes mottled with white, or more rarely with red spots. Microscopically we can see that the lesions are situated toward the portal spaces and around the lobules, that leucocytes abound, and that the cells are often in a condition of fatty degeneration.

A chemical examination shows that there is a slight diminution of water, an increase of fat three times beyond the normal, and usually an increase in the amount of albumin.

The conditions which produce these lesions are numerous and complex. Their gravity may be held to be in direct relation to the duration of the disease, but there are so many exceptions that one might almost be led to hold the opposite view. Thus, in a case in which death occurred from scarlatinal nephritis after a month of the disease the liver was found to be almost normal, while in other cases of extremely acute course there were lesions of the most extensive and profound degeneration.

No less important are the lesions found in erysipelas, and in all streptococcal infections. In fact, the hepatic lesions play an important part in the development of erysipelas; certain grave symptoms which appear in this infection are indeed owing to previous lesions of the liver. Many observers have borne witness to the gravity of erysipelas in hepatic patients. There is a difference, however, in the influence exerted by the various affections of the liver. If the cell itself is relatively normal, as in hypertrophic biliary cirrhosis, recovery is the rule; but if the cell is much altered, as in certain forms of atrophic cirrhosis, a fatal issue is certain. Bridiers collected ten cases of ery-

sipelas which occurred during the course of hepatic cirrhosis, all were fatal. Roger and Garnier have always laid stress on the part played by hepatic lesions in the causation of the delirium of erysipelas, and even more in delirium tremens. Starting from their clinical observations, they made anatomicopathological investigations of the liver in erysipelas, and in streptococcic infections in general. The liver under these conditions presents almost specific lesions, which differentiate it from other infected livers, the chief difference being that the changes are uniformly disseminated throughout the lobule, and are less profound and less intense than in other infections, as, for instance, in scarlatina. There would seem to be a difference in the hepatic lesions following streptococcal infection in adults and in children; they are less severe in the latter, and the cells appear to offer more resistance than adult cells to the streptococcal toxins. We may, therefore, conclude that the liver is not only affected by the streptococcus, but may, when for any reason it is in a condition of functional insufficiency, injuriously affect the course and the prognosis of the infection.

These researches, which are daily assuming greater and more extensive proportions and importance, throw much light on the course and the issue of acute infections, and demonstrate how the liver, although it exercises a protective influence over the system, is very easily affected by pathogenic organisms, and may by its functions modify and aggravate the prognosis of infections.

General Symptomatology.

Auscultation of the Liver.—In the last few years Piazza-Martini has called attention to a venous murmur heard sometimes over a more or less extensive area, usually limited to the anterior abdominal wall, a murmur not to be confounded with the one observed in some cases of cirrhosis, which is due to the development of a venous network in the substance of the abdominal wall itself, or in front of the parietal peritoneum from obstruction to the portal circulation, nor with the one heard over the hepatic area, caused by compression of the trunk of the portal vein or one of its branches (Gabbi). The murmur under consideration has been heard by Piazza-Martini in six cases, one of primary carcinoma of the liver, four of interstitial hepatitis, and one of chylous effusion from carcinoma of the mesenteric glands.

It is subject to variations in intensity especially during the act of respiration, being increased by inspiration and diminished by expiration, while it decreases and sometimes disappears entirely after paracentesis. As a rule, it is heard in the sixth right intercostal space, between the anterior axillary and the midclavicular lines, sometimes in the fifth or in the seventh space, rarely over the right costal arch

and the prolongation of the anterior axillary, most rarely under the right costal arch. This murmur, as has been shown by necroscopic examinations, has its origin in that part of the vena cava which is in relation to the liver, and not in other veins. It is certainly due to a narrowing of the lumen of the inferior vena cava caused either by external pressure, or by rotation of the liver from left to right (owing to the presence of ascitic fluid or to the coexistence of hydrothorax), this causing a straining of the vena cava by means of the suprahepatic veins, which are displaced with the gland. In some cases the constriction of the vena cava is due to a neoplasm, developed within the lumen of the blood-vessel itself. This murmur may be of importance in the diagnosis of the seat of tumors developing on the inferior surface of the liver.

General Therapeutics.

The chief object of modern experimental therapeusis of the liver is the compensation for or the overcoming of the hepatic insufficiency which is always present and menacing in diseases of this organ. To this end various means have been proposed which, it must be acknowledged, have not always fulfilled the hopes held in regard to them.

We have already spoken of the importance in hepatic diseases of reducing the fermentative and putrefactive processes which develop in the intestines (the latter being notably altered in their functions by the hepatic lesion), and cause the formation of toxic substances which can no longer be arrested, transformed, or eliminated by the parenchyma of the liver; and we have in this connection criticised the use of insoluble antiseptics, so widely employed in practice for the purpose of disinfection.

The most efficacious intestinal antisepsis is beyond a doubt obtained by a milk diet; of drugs, the one best deserving confidence is an alkaline hyposulphite, proposed by Semmola. In 1896 the value of this remedy was confirmed by the interesting experimental studies of Heymans and Masoin. These authors investigated the antitoxic action of sodium hyposulphite on the dinitryls, and they demonstrated that the injection of hyposulphite of sodium had a preventive and curative effect in such poisoning. These interesting studies demonstrate the importance of the administration of alkaline hyposulphites, either internally or by enteroclysis, in the treatment of intestinal infections and for the disinfection of the gastroenteric tract.

It would, however, be more to the point did we possess the means of destroying the toxic products after they have entered the circulation. Oxidizing agents have been tried (A. Robin) by means of inhalations of oxygen, the use of the benzoate of sodium or of lithium, etc.; but we must not build too many hopes upon these remedies, for

their use may or may not be founded on correct theories, and cannot as yet serve for a system of rational therapy.

A more easily attained object is that of effecting the elimination of the poisons already absorbed. Evacuation meets this indication to some extent, since a portion of the poisonous matter is certainly eliminated through the intestines, but much the larger part is eliminated through the kidneys, so that we must secure active diuresis if possible. Milk is indicated for this purpose, and frequent enemata of cold water are of use. Finally the skin, while less active in the elimination of poisons than the other two emunctories, is not to be neglected.

The foregoing are the chief means at our disposal for the overcoming of autointoxication. But therapy is capable of better things, because it can act directly upon the hepatic cell to the improvement of its functional powers. Very little is known in regard to substances capable of increasing glycogenesis. Carbohydrates certainly appear to possess that power, and recent researches seem to indicate that alkalies and antipyrin also possess it. Finally, we must bear in mind that to increase the uropoietic functions we can always have recourse to hygienic and dietetic measures.

These methods of treatment, however, have a merely indirect action on diseases of the hepatic gland, since they can only succeed in preventing the accumulation of toxic matters in the organism, or in overcoming the functional insufficiency of the liver. Diminished hepatic functions not only produce an accumulation of noxious substances in the body, but also deprive the economy of the useful substances which are produced by the liver.

From this point of view it has been the aim of the profession from the beginning of the last century to administer some substance to the patients which would represent the active principles of the bile or of urea, for which purpose bile in the form of extracts of ox gall, or its salts, was given. Bile not only acts chemically, taking the place of that which has not been secreted by the liver, but has a cholagogue action far greater than that of any other remedy. So that the use of bile extract, and, above all, of its salts (0.30 to 1.50 gm. of sodium choleate), may be of use, and has recently been recommended by Stadelmann; taken by the mouth, however, it possesses the disadvantage of causing nausea and gastric disturbances, and when injected by the rectum is irritating and not absorbed. As to urea, so much extolled by Klemperer, Kolisch, Strauss, and Beckert in cases of cirrhosis, it has proved but a feeble diuretic in the hands of Frutran, Kolm, Sabrezès, and Dion. It possesses the advantage of being innocuous even in large doses (15 to 20 gm.), and is usually well tolerated by the stomach.

Quite recently a further step in advance has been taken by the ad-

ministration of hepatic gland extract, a practice based on the theory of internal gland secretion propounded by Brown-Séquard. In other words, the idea is that hepatic insufficiency may be due to a diminished or abolished secretive power of the hepatic cell, and by means of opotherapy the products of hepatic activity, which are no longer provided by the diseased hepatic tissues, are supplied. By this form of treatment many have obtained improvement not only in atrophic cirrhosis, hepatic syphilis, cancer of the liver, and cardiac liver, but also in diabetes and gout. Gilbert in especial has turned his attention to opotherapy in diabetes mellitus, and has found that the ingestion of hepatic substance modifies the amount of sugar in the urine in a certain number of cases. The effects vary according to the case. He holds that there is the most improvement in cases of diabetes connected with functional insufficiency of the liver. But when the glycosuria depends upon hyperactivity of the liver, there will either be no improvement or an increased elimination of sugar. Hepatic opotherapy would thus appear to be not only a valuable remedy in certain cases, but a means of differential diagnosis between diabetes from hyper- and hypoactivity. The powder or the extract of beef or pig's liver may be used, mixed with milk, and it may be given by the mouth or in clysters, and the extract can also be given hypodermically. According to Gilbert and Carnot, the action is one of stimulation to the secretion of bile, rather than that of supplying the secretory products contained in the extract of liver; it also increases the functional activity of the cells, and of glycogenesis in especial. Finally it would appear to help in the regeneration of the liver tissues. These encouraging results of experimentation are certainly worthy of consideration; but the method is too recent a one for a definitive opinion to be given as to its value. As Gilbert and Carnot have shown, true hepatic opotherapy will not exist until we have learned how to separate the noxious from the useful elements in the liver; for, truth to tell, the hepatic extract does possess some toxic properties. Mairet and Vires have found that an endovenous injection of aqueous extract of liver is fatal to rabbits, producing exophthalmos, slowing of the respiration, hypopyresis and diarrhœa, somnolence, and convulsive attacks. The lesions found post mortem were congestion of the various organs, especially of the digestive tract and coagulation of the blood in the heart and veins. The toxic action is, however, not entirely due to the coagulating power. These investigators, in fact, demonstrated that by means of heat the coagulating property of the toxic matter could be abolished. By heating the extract a precipitate is obtained which kills by coagulation, the power of which is weakened by a constantly increasing temperature, and disappears at 100° C., while the filtrate possesses toxic properties, since it is capable of causing the death of

the animal, inducing myosis, slowing of the respiration, meteorism, diarrhœa, etc.; death usually occurs without convulsions, and at autopsy the heart and vessels do not contain coagula. The liver, therefore, must contain substances which have the power of coagulation, and toxic products; heat attenuates and abolishes the former, alcohol after a long time destroys both.

These properties appear to be due to albuminous substances, for a nucleoalbumin has been isolated from the coagulating principle, and an alkaloid toxin and soluble ferments from the toxic principles.

Hepatoptosis.

The value of surgical intervention in hepatoptosis, which was first introduced by Marchand and performed on a woman of thirty-seven years, has in the last few years received notable indorsement from the results of experimentation. Marchand's process consists in the insertion of silk threads through the organ, on both the right and left sides, about 4 cm. from its anterior border, and in the fixation of these ligatures to the parietal peritoneum.

Up to the present time fifteen cases have been reported of intervention by this process, in more or less modified form, and out of eleven cases described at length by the writers there were eight recoveries, one death, and two uncertain results.

D. Giordano, in a case of hepatoptosis complicated by uterine fibroma, modified the process in the following manner: Having opened the abdomen by an oblique incision, which extended for 12 cm. along the right costal border, he cut off the umbilical portion of the suspensory ligament, which was markedly elongated, and inserted a stitch of strong catgut through the xiphoid cartilage and the longitudinal ligament at its point of attachment to the anterior border of the liver; other stitches were inserted anteroposteriorly as far as he could reach, some going through the longitudinal ligament and some along the costal border, crossing above or perforating the costal cartilages. The convex surface of the liver was then touched with crystals of carbolic acid, and the various stitches were tied. The first stitch secured the anterior margin of the liver to the xiphocostal angle, the others, by pulling on the longitudinal ligament, uplifted the posterior margin, and also diminished rotation of the viscus. Taking advantage of the fact that the hepatic border over the gall bladder is poor in parenchymatous and rich in connective tissue, he inserted another strong catgut suture and fastened it to the last rib. The result obtained by the operation was thoroughly satisfactory, and when the patient was seen two months later there was no displacement of the liver at all. More recently Santucci has further simplified the method,

and in a case of cirrhotic hepatoptosis he merely scraped the serous covering of the convex surface of the liver and extirpated the parietal peritoneum, in order to produce adhesions between the liver and the anterior abdominal wall.

This method can well be applied if the liver is reduced in size and consequently in weight, by a progressive cirrhotic process; but it does not seem to suffice in the case of a displaced normal liver. In any case, surgical intervention is indicated only when there are marked functional disorders and severe colic, and when the general condition of the patient is good enough to support so severe an operation.

Suppurative Hepatitis.

The etiology of hepatic abscess has always attracted the attention of bacteriologists, who of late years have endeavored to reproduce it in animals, by using microorganisms that have been supposed to be causes of hepatic suppuration, especially the bacterium coli, which by the fact of its constant presence in the intestines might be considered to be the proximate etiological factor. Castellani has taken up the matter experimentally, and has come to the conclusion that it is not possible to produce liver abscess with the coli bacillus, by introducing it into either a normal or a diseased intestine or into a vein leading directly to the liver, even though traumatic lesions are thereby caused in the hepatic region. These lesions are indeed of an entirely different nature, and may produce circumscribed areas of necrosis.

De Vecchi, starting from the idea that the liver is endowed with important powers of defence against microorganisms, has taken up the question in his turn, and has endeavored to ascertain whether it is possible to cause the formation of true liver abscesses by means of the coli bacillus, if biliary stasis be first produced by ligature of the ductus choledochus. The results obtained were positive, the typical lesions of suppurative hepatitis being produced whether the germ was introduced into the ductus choledochus, or ingested, or injected directly into a branch of the portal vein. There was merely a slight difference in the intensity and the disposition of the abscesses according to the method used.

In 1897 Korn made a study of the bacteria found in the pus of an abscess contracted in Sumatra, and found in conjunction with the streptococcus a bacillus which occurred in colonies of a yellow color, and at first appeared to be the typhoid bacillus, because it could not be stained by the Gram method, and because it had an analogous morphology; it was capable of producing local suppurative phenomena, which, however, very quickly underwent retrogressive changes. One curious and interesting fact was that, in spite of the most careful

asepsis, and even when it was certain that the bacillus had been perfectly isolated, streptococci often developed at the point of injection. This would seem to indicate that the streptococcus, often inactive alone, found in the bacillus a symbiosis which not only made it develop more readily in a given point, but increased its virulency. In regard to abscess of the liver, the most plausible explanation of the mechanism is that the bacillus passing through the solutions of continuity in the intestines is retained in the liver, where it prepares a suitable field for the growth of the streptococcus.

Korn, however, does not clearly describe the individual characteristics of the bacillus which he found, nor does he state whether there are valid reasons for excluding the possibility of its being the coli bacillus. The fact that it resembled the typhoid bacillus, and that it did not react to the Gram method, would lead to the supposition that it was the coli bacillus, whose polymorphism is well known.

In 1897 Hassler and Boisson came to the conclusion that the most constant and pathognomonic *symptoms* of hepatic abscess are a special resistance of the organ to palpation (like that obtained by pressure on a rubber ball with thick, tense walls) and a very fine crepitation perceived by touch and by auscultation either when pressure is made by the hand or during the act of inspiration. But in a case of carcinoma of the liver secondary to cancer of the stomach Cantù found the same symptoms. So that in reality they merely indicate softening in some portion of the hepatic parenchyma independent of abscess formation. There is as yet therefore no sign pathognomonic of liver abscess, and its diagnosis rests upon a clinical observation of the patient and a careful study of the history. Moreover, the raising of any one symptom, no matter how important, to the dignity of a pathognomonic symptom in any disease, is no longer considered admissible in practice.

According to the observations of Josserand, dysentery plays an important part in the etiology of suppurative hepatitis. He has noticed that dysenteric abscesses may occur in the liver as long as ten years after the real or apparent cure of the enteritis. Consequently, if we have to do with a patient suspected of having hepatic suppuration, a history of dysentery should be sought for with the greatest care. In these cases of tardy dysenteric abscess the period of apparent health between the recovery from dysentery and the appearance of the abscess is often marked by slight or severe intestinal disturbances. It is probable that the germs destined to cause the hepatitis exist in the intestines; in fact, Josserand was able to find dysenteric residua at the autopsy when there had been no intestinal symptoms during life. Intestinal symptoms in patients who have suffered from dysentery should, however, be carefully watched for, because the fact that the dysentery is of ancient date is no guaranty of security for the future.

Hepatic Cirrhosis.

Etiology of Venous Cirrhosis.—Clinicians and investigators have long given their attention to the question of the etiology and the pathogenesis of venous cirrhosis, and in especial have they endeavored to ascertain the effect of wine in determining the sclerotic process, and whether among the ingredients of wine it was the alcohol which induced inflammation of the periportal connective tissues.

In 1897 Lancereaux presented to the Paris Academy of Medicine the result of his studies in regard to the cirrhosis of wine drinkers, and showed that the injurious effects of wine were quite as great as those of spirits, especially if the wine were plastered. He was led to a study of the subject by observation of the fact that symptoms of chronic alcoholism were absent in patients affected by cirrhosis of the liver, whose history merely showed an abuse of wine drinking, as much as six litres a day having been taken in some cases. This theory receives confirmation from the relative frequency with which cirrhosis is met with in certain wine-growing countries where alcoholism is, so to speak, unknown—in comparison with other parts of France, as, for instance, Normandy and Brittany, where wine is scarcely drunk at all and alcohol is consumed in quantity. Lancereaux endeavored to ascertain what was the noxious ingredient in wine which was capable of causing hepatic sclerosis, and gave his attention to the salts of potassium, which are found in relatively large amount in certain wines and beers. To discover what influence these salts have on the liver, he took guinea-pigs, rabbits, and dogs, and mixed about 2 to 7 gm. of the bisulphate of potassium with their daily food. The larger number of these animals died in from six to eighteen months from the beginning of the experimentation, and all exhibited, though in varying degree, lesions of bivenous sclerosis, absolutely similar to those found in wine drinkers. Thus it would appear that the salts of potassium contained in wine exercise a direct action on the walls of the intrahepatic branches of the portal vein and on the surrounding connective tissue. Naturally "plastered" wine is more injurious than pure wine, a fact demonstrated by the frequency of cirrhosis in those who drink Parisian wine, which has usually been plastered, *i.e.*, treated with gypsum to neutralize the acids.

Laborde opposes these conclusions, holding that the experimental and statistical data of Lancereaux do not prove that sclerosis of the liver is due to the gypsum. Rabbits should not have been chosen for the experiments, their livers being easily affected by the most diverse causes. The most reliable way would be to take a dog and introduce a certain amount of gypsum by means of a stomach tube, and we

should then observe how well it tolerates both chalk and the bisulphate of potassium without the production of a single morbid symptom.

Lancereaux's theory is not accepted by the majority of pathologists. It seems to us, however, that even if we are unable to exclude the influence of the alcohol contained in the wine from the etiology of cirrhosis, the adulteration of wine and its plastering may represent a factor not to be neglected, and this further emphasizes the necessity for rigid hygienic measures in regard to the adulteration and the sale of wine in large cities.

The question of the mode of action of alcohol on the liver—that is to say, of the mechanism of alcoholic cirrhosis—which has been so widely discussed, and the subject of such contradictory theories, has of late years received valuable contributions from the researches of Inghilleri. He came to the conclusion that alcohol is not the chief cause in the production of venous cirrhosis, but that it merely produces a condition of insufficiency in the cell, a predisposition to disease, and also imparts activity to the cause or causes of cirrhosis, among which the one of chief prominence is the disturbed gastrointestinal chemism. In other words, the influence of alcohol in the etiology of cirrhosis may be compared to that of cold in rheumatism. In a final series of researches he was able to cause chronic gastritis in animals by the use of alcohol and other irritating substances. Inghilleri is inclined to believe that the gastric lesions caused by the abuse of alcoholic matters constitute an essential condition in the pathogenesis of venous cirrhosis, because they produce abnormal fermentation in the gastrointestinal tract, whose products may be absorbed and in passing through the liver may induce the typical proliferation of connective tissue, and consecutive sclerosis.

Alcohol, then, would appear to be the initial cause in the pathogenesis of cirrhosis, but it does not produce the disease directly—rather it leaves the direct action to the toxic products (normal or pathological) of gastrointestinal chemism. This throws light on the cases of cirrhosis in which no history of alcoholism can be traced.

Venous Cirrhosis, as we have before stated, is frequent in adults, but very rare in children, and when met with is due to an excess of wine or liquors, carelessly allowed by their parents. Of late years cases have been reported, in some of which an alcoholic etiology could be traced, but in many was entirely absent, nor could any history be found to account for the trouble except that of some previous infection. Cases of cirrhosis in children will be more frequently recognized when physicians divest themselves of the notion that sclerotic induration of the liver is exceptional in early life.

Pigmentary Cirrhosis.—This form of cirrhosis has been recognized

for some time, but it is only of late years that it has been extensively and minutely studied.

The discussion which took place in the Medical Society of the Paris hospitals is well known; three cases of diabetes were reported by Rénon, Massary, Jeanselme, and Tenneson, and two by Letulle, one of which was of alcoholic origin and the other was coexistent with primary cancer of the liver. This form, which anatomically and clinically is confounded with ordinary cirrhosis, is characterized by the dissemination of a ferruginous pigment throughout the body, but more especially and abundantly in the liver, pancreas, and heart, less being found in the kidneys. Abbott had the opportunity of studying the special pigment in one of his cases, and in respect to the size and the tint of pigment granules distinguished two kinds—one of a dark brown, the other of a light yellow color. Both contained iron, but in the first, composed of hæmatosiderin, the iron was easily demonstrated by the ordinary reactions, while in the second, made of hæmatofuchsin, it was necessary first to break up the ferroorganic molecule by means of hydrochloric acid and heat. According to Abbott, the new formation of connective tissue and the resulting hepatic sclerosis are due to the production of pigment—the pigment is the primordial fact and the chronic hepatitis merely the result. A consideration of many observations of this affection, including his own case, convinced him that a predisposition to hemorrhages is always found in the history of the patients. So it would appear that the primary cause of the cirrhosis is capillary hemorrhage into the parenchyma of the liver; the resulting destruction of the blood cells causes the formation of pigment within the hepatic cells, which undergo a necrobiotic process, and the pigment is thrown out into the interstitial connective tissue, which thus undergoes a process of proliferation followed by sclerosis.

French authorities, on the other hand, regard the pigment merely as melanin, and Gautier thus explains its origin: The liver normally forms pigment from the hæmoglobin; when it is diseased, it is able to produce only a modified pigment, sometimes only ferruginous pigment, which is deposited in various organs. According to this theory, pigmentation is the result and not the cause of the hepatic disorder. In favor of this hypothesis we have the fact that the pigmentation of the lymphatic glands in the vicinity of the hilum of the liver is more intense than that of more distant glands. This interpretation of the matter is the more comprehensible, and is further upheld by the fact that the occurrence of parenchymatous hemorrhages referred to by Abbott is not corroborated by the data, and is merely an arbitrary hypothesis.

Some have held that this form of cirrhosis depends absolutely upon diabetes; but many of the recently reported cases forbid this view.

Letulle holds that, in cases of bronzed diabetes, in which pigmentary cirrhosis exists, the coloration of the skin is due to the deposition of melanin in the sudoriferous glands and the Malpighian stratum of the epidermis.

This pigmentary form of cirrhosis has merely an anatomicopathological interest, its symptoms, course, and therapy being those of ordinary cirrhosis. Only when it is combined with diabetes does the nosology become complex and the prognosis more grave.

Compensatory Hypertrophy of the Liver.—A much-disputed point in physio-pathology is the possibility of the regeneration of the liver in destructive diseases of this organ. Naturally the curability of certain hepatic affections, and of cirrhosis in especial, would be closely related to the compensatory power, which, according to the researches of certain investigators, can be exercised by the hepatic gland. Many have been the experiments directed to the discovery of this power.

It having been established that the liver of animals is capable of regeneration, an effort was made to ascertain whether the same occurs in man in diseases which destroy the hepatic parenchyma, and the first affection taken for a subject of investigation was that of hydatid cyst, a lesion which, while it may destroy a portion of the liver, does not produce serious alterations in the remainder. During found that when there is a large cyst which destroys a great part of one lobe, the other lobe of the liver is always hypertrophied; Duplay observed that when the cyst is extirpated, the liver very soon regains its former size; Letulle had the opportunity of examining at autopsy a liver, from which he had removed a large cyst, and found that the organ was of its normal size and shape.

Ponfick, on the other hand, by histological researches in similar cases found that the normal structure of the liver was modified; that the trabeculæ were no longer arranged in ray shape; that the cells were irregularly disposed, and that the capillaries were sinuous.

This important subject has been studied, not only in the case of hydatid cysts, but also in hepatic cirrhosis, which in the end causes atrophy and destruction of the hepatic cell, and several authorities have reported cases in which hypertrophic increase in size of one lobe corresponded to the atrophy of the other.

An important contribution to the subject was made in 1897 by Zadoc-Kan, who studied the reproduction of the liver in hypertrophic alcoholic cirrhosis, from both the histological and the functional standpoint. By a histological examination he was able to find irregular groups of cells in process of karyokinesis; by the functional, he showed that the biligenetic, urogenetic, glycogenetic, and protective functions of the liver were unimpaired or only very slightly affected.

Greco in 1899 made a histological study of other diseases of the

liver, and reported his observations in regard to hypertrophic tuberculous cirrhosis, cirrhosis secondary to nodular carcinoma, and hypertrophic malarial cirrhosis. In all three cases he found a true cellular reproduction. In the midst of, or near to, the degenerated portion, one or more groups of cells could sometimes be observed which were in evident contrast to the neighboring tissues. These cells were arranged irregularly and not in the manner typical of the structure of the hepatic lobule; they were larger than normal, and were sometimes undergoing segmentation. Their nuclei were also larger than normal, and were sometimes undergoing karyokinesis. Here and there could be noted the neoformation of biliary vessels.

Finally Reinecke, in a case of hepatic syphilide and in another of echinococcus of the right lobe of the liver, found definite signs of more or less atypical reproduction of the parenchyma of the liver.

From an anatomicopathological point of view, these researches appear to demonstrate the possibility of regeneration of the liver in affections which are of a character to destroy this organ.

But is this matter of any practical importance? If it were possible, especially in cirrhosis, to arrest the process by rational therapeutic intervention, and to reproduce the hepatic cell as well, we could obtain a cure of the disease in the true sense of the word. And although this is not the rule in clinical practice, yet it is not absolutely unknown. The successful cases in the treatment of atrophic cirrhosis demonstrate the practical bearing of these observations, and are also more easy of comprehension, because of them; while the prognostic and therapeutic indications upheld by Semmola before these researches had given any positive results receive confirmation and support from both experimental and anatomicopathological investigations.

The Pancreas in Hepatic Cirrhosis.—An anatomicopathological study worthy of note has been made by Lefas on the condition of the pancreas in cirrhosis. In atrophic alcoholic cirrhosis the pancreas appeared to be enlarged; but if the different parts of the organ were carefully observed, it was found that there was atrophy of the body and of the head relatively to the size of the splenic end. The color was of a grayish-yellow, like wax; the consistency increased. The microscope showed that there was an interlobular sclerosis which started from the blood capillaries, but in very advanced processes reached to the arteries and the veins, while those of the liver were not in the least abnormal. The most important lesions of the cells were fatty degeneration, which was marked and constant, and pigmentation, which was rare.

In hypertrophic cirrhosis the volume of the pancreas is not increased; in consistency it is resistant without being hard; in color a yellowish-white. The interlobular connective tissue is increased and

thickened, especially around the excretory ducts, the coats of which are greatly thickened. There is also a certain amount of intralobular sclerosis. The epithelium of the ducts shows only a slight amount of proliferation. The acini are invaded by embryonal cells, and here and there show signs of granular degeneration.

In cardiac cirrhosis there is not, properly speaking, a cardiac pancreas, but in some cases it shows certain special characteristics. Around the smaller arteries and excretory ducts there is a connective-tissue proliferation which tends to form fibrous lamellæ, and around these plaques there is a certain amount of sclerosis. The excretory canals, on the other hand, apart from a slight cellular proliferation, appear to be in good condition. In the parenchyma the fatty degeneration is not marked. But there is an irregular proliferation of the nuclei in the granular acini.

The pathogenesis of these secondary cirrhotic processes in the pancreas varies according to the form of the hepatic cirrhosis. In alcoholic cirrhosis it may originate from thrombosis of the intralobular capillaries. In alcoholism liver and pancreas go *pari passu* in regard to connective-tissue and cellular changes. In hypertrophic cirrhosis the connection is less close, but the pancreatic lesion is of the same type as that of the liver—in other words, of the embryonic type. The pathogenesis of cardiac sclerosis of the pancreas is the same as that of the liver—that is to say, it is due to prolonged venous stasis.

The researches of Læfas, published in 1900, have not as yet received confirmation, but they merit the attention of the pathologist who desires to ascertain how much and in what way the functional powers of the pancreas are modified in cirrhosis, a subject which is at the present time entirely neglected. The semeiology of the pancreas is, however, still in its infancy, and nothing at all is known in regard to the diagnosis of chronic pancreatitis, which often escapes observation and is recognized only at the autopsy. When we are better informed in regard to this matter, it may be that a great light will be thrown on hepatic semeiology.

Acute Cirrhosis.—The cases in which cirrhosis of the liver is rapidly fatal, while not altogether rare, are still somewhat exceptional. Frerichs was the first to report cases in which death occurred after one or two months, but they were accompanied by prominent cardiac and pulmonary symptoms, etc. Bamberger in more recent times has decided that the maximum duration of the disease is three years and the minimum seven weeks; the average would be about a year. Stricker and Weisberger observed death in the sixth week; and in a case of Freyan, complicated by grave icterus, it took place in a month. Eichhorst reports a case in which the whole course of the disease appears to have taken only two weeks.

As we have already pointed out, Hanot believes that these occurrences are the result of acute yellow atrophy attacking a liver which was already cirrhotic. Other cases of an acute course of the disease have recently been reported. The mechanism of death in these cases would seem to be an autointoxication, and this theory is corroborated by the appearance of parotiditis toward the end.

Arterial Pressure in Cirrhosis.—Important contributions have been made to the study of the symptomatology of cirrhosis from the researches on arterial pressure and on metabolism.

Gilbert and Garnier found in every case of cirrhosis that they examined a marked lowering of arterial pressure. Instead of being from 170 to 150 mm. of mercury, which is normal, it varied from 100 to 140 mm. This pressure condition is most marked after paracentesis, and becomes lower every time the operation is repeated. Pathogenically the hypotension accompanying ascites should be distinguished from that of the terminal period of the disease, which is due to cachexia. A knowledge of this symptom may in doubtful cases assist in the differential diagnosis of cirrhosis from that of chronic peritonitis.

The cause of the lowered arterial pressure is to be found in the mechanical impediment to the portal circulation due to the development of the hepatic sclerosis. It is well known that ligature of the portal vein of an animal will cause a rapid lowering of pressure.

Metabolism in Venous Cirrhosis.—At the Italian Medical Congress of 1898 Calabrese reported some of his researches into metabolism in venous cirrhosis, and reached the following conclusions:

1. In hepatic cirrhosis the absorption of nitrogenous matters and fats is interfered with in direct ratio to the severity of the disease.

2. Absorption is so greatly improved after evacuation of the ascites that the disturbance may well be considered due chiefly to the venous stasis produced in the intestines by pressure of the ascitic fluid.

3. In cirrhosis at an advanced stage there is no pathological destruction of the albumin of the tissues, but a moderate retention of nitrogen, which increases markedly after evacuation of the fluid. As the amount returns to its first degree after reformation of the fluid, it is fair to infer that the retention of the nitrogen is for the benefit of the ascites, because if the patient is kept on an insufficient diet the albumin of the ascites, which is again collecting, can be derived only from the albumin of tissues, whence the tendency to marasmus after repeated punctures.

4. In cirrhosis there is constantly: (*a*) diminution of the ureal nitrogen, and therefore of urea, both as to the amount passed daily and as to the proportion of the ureal nitrogen to the total nitrogen; (*b*) increase of the non-ureal nitrogen; (*c*) absolute and relative increase of ammonia.

5. If ammonia be administered in the form of a carbonate to a healthy individual, it is completely transformed into urea; in two patients suffering from beginning cirrhosis it was only partly transformed, and in a patient with advanced cirrhosis it was not transformed at all.

The last two occurrences might be due to the altered functional powers of the liver, to which is chiefly owing the formation of urea and the transformation of the carbonate of ammonium into urea. But we must keep in mind that the amount of ammonia in the urine depends exactly upon the amount of acid which is formed in the organism. Therefore the obstructed or diminished formation of urea in cirrhosis might depend upon the acidification of the organism. In cirrhosis there is a constant increase in the acidity of the urine. This, however, may merely be an accessory fact, because the first explanation seems to be much the clearest and the most admissible, sustained as it is by all the knowledge we possess in regard to hepatic urogenesis.

Splenic Tumor in Biliary Cirrhosis.—Obscurity still surrounds the pathogenesis of splenomegaly, that symptom which is so all-important in biliary cirrhosis, and yet the contribution to its elucidation made by Gilbert and Lereboullet is of great value. From the result of their researches it would appear that the splenic hypertrophy is due to two concomitant causes: infection and passive hyperæmia. The latter certainly occurs whenever there is the slightest obstruction to the portal circulation, as in the forms of cirrhosis under discussion, and this is demonstrated by the fact that the splenomegaly is reduced by one-half under the influence of subsequent gastrointestinal hemorrhages.

But infection also occurs, and therefore we must admit a direct infection of the spleen, depending, however, upon primary infection of the liver, for we frequently observe a marked increase in the size of the liver during the course of an infective angiocholitis. This double origin is sustained not only clinically but experimentally.

It is probable that the infection takes place by means of the splenic vein. But obstruction to the flow of the splenic circulation is so promptly responsive to circulatory disorders in the liver that during digestion under physiological conditions there is a slight increase in the size of the spleen. It may be, therefore, that, as in the case of the suprahepatic veins, there is a retrograde infection in the splenic vein, especially if the microorganisms possess motility.

The Surgical Treatment of Venous Cirrhosis.—Impeded circulation in the venous portal system is one of the gravest consequences of the cirrhotic process in the liver. The dangerous results of portal hypertension are ascites, gastric, œsophageal, and intestinal varices, hemorrhoids, grave gastrointestinal hemorrhages, and finally, arterial

hypotension, which brings with it tachycardia, oliguria, and all the symptoms of cardiac weakness. Now, any one of these symptoms or any combination of them may at any time endanger the life of the patient. In practice it is frequently found that when the ascites is of sufficient extent to produce great endoabdominal pressure there are symptoms of pressure on the stomach and the intestines, giving gastric intolerance and obstinate constipation; on the arteries and veins of the kidneys, resulting in marked oliguria; on the inferior vena cava, with marked œdema of the lower extremities and scrotum; also compression of the diaphragm, which, besides causing enlargement of the base of the thorax and upward displacement of the ribs, produces grave respiratory and cardiac disorders, so that abdominal paracentesis may have to be promptly resorted to at any time to save the patient's life.

The rational cure of the ascites has of late been absorbing the attention of practitioners, whose endeavor it is to ascertain whether it is possible to diminish the tension in the portal circulation by opening out another channel for the blood—in other words, by introducing the blood from the branches of the portal vein into that of the inferior vena cava. The object of this procedure is to imitate the natural compensation which in this disease is formed by the development of a collateral circulation. In the general part of our treatise (see anatomical signs) we mentioned the so-called accessory portal veins of Sappey, which, in case of obstructed portal circulation, take on a greater development and constitute a secondary route for the portal blood, and under the head of venous cirrhosis we stated the diagnostic and prognostic importance of the development of the *caput Medusæ*. Therefore the attempt has been made to compensate for the ascites and the other symptoms due to obstructed circulation of the portal vein by operative intervention capable of causing greater anastomoses between the venous branches of the portal vein and the superficial abdominal veins tributary to the inferior vena cava—thus carrying out the great precept of Hippocrates: *quo natura vergit, eo ducere oportet.*

Many observers (Strümpell, Moadonel) had already noted that in some cases after repeated puncture the ascites did not return. In one case it is even said that the patient lived twenty years, and that then his death was not due to cirrhosis of the liver. Numerous observations in the domain of surgery had confirmed the possibility of the formation of new vessels, along the peritoneal adhesions, which were often of a considerable size. Moreover, the post-mortem examination of several cases of ordinary cirrhosis without ascites showed two essential characteristics: in some the viscera were adherent to the abdominal walls by means of vascularized connective-tissue bands; in others there was a marked increase in the capacity of such of the veins of

the portal system as anastomosed with others of the general system. These anastomoses were between the veins of the round ligament of the liver and the left branch of the portal vein, and the epigastric and other veins of the abdominal walls; between the subperitoneal veins that run within the folds of the hepatic ligament and the phrenic vein, the vein of Glisson's capsule and the large vena azygos; between the inferior mesenteric veins and the iliac through the hemorrhoidal plexus (accessory vena porta). The formation of a similar circulatory medium may be observed in the living subject in the superficial veins of the abdominal walls, and in the *caput Medusæ* around the umbilicus. Clinical and anatomicopathological observation gave Talma of Utrecht the idea of inducing the anastomosis of the portal vein, not with the vena cava (an operation which Eck, Massen, Pavlov, and Queirolo had performed with the greatest difficulty on animals, and which has never been attempted on man), but with one of its chief collateral veins, the gastroepiploic. He recommended this operation, which was given his name and which was performed for the first time by Menlen in 1889 and later by Schelkly in 1891. But as both of the patients operated on died, the procedure did not arouse much enthusiasm, and fell into oblivion until Talma restored it to an honorable position by a second article on the 30th of July, 1900, in which he reported several cases of cirrhosis which had been cured by its means. Talma's operation consists of a simple laparotomy in the linea alba with suture of the omentum to the anterior parietal peritoneum. It has been modified by Morrison, who proposed rubbing the surface of the liver, spleen, intestinal mass, and parietal peritoneum with aseptic sponges, and then suturing the omentum to the peritoneum of the abdominal wall. This rough handling of the visceral serous membrane favors the formation of adhesions between the visceral and the parietal peritoneum, which is the object of the operation. Clemente proposed another modification of Talma's original operation. To assure fully the adhesion and consecutive development of veins between the great omentum and the parietal peritoneum he first makes an incision extending from the ensiform cartilage to the umbilicus, and then dissects the parietal peritoneum all about the wound for a distance of about three finger-breadths; as much of the great omentum as can be displaced is brought out toward the lower end; the abdominal cavity is closed by suturing the borders of the peritoneum, and then the great omentum is spread out between the detached peritoneum and the surface of the abdominal wall, its margins being attached to the periphery. Finally the linea alba and then the skin are closed by means of separate sutures.

Pascale, of Naples, recently made extensive experimental researches on dogs to ascertain how much might be expected of Talma's proc-

ess in the development of an adequate collateral circulation. He came to the conclusion that the vessels develop very little in contact with the aponeurosis, but much more when the epiploon comes in direct contact with the subperitoneal and intramuscular connective tissue. In well-prepared sections from these cases he traced the passage of the large vessels of the epiploon into the intermuscular spaces, in which the veins appeared like a network filled with blood. These data were confirmed on man, in the case of patients operated on by him, by a modified process of his own, which consists of: 1. Median laparotomy in the umbilical region, including in the incision the fibrous part of the linea alba, and the umbilical cicatrix, which is removed. 2. Along and by the side of the whole abdominal incision, and above and below the former situation of the umbilical cicatrix for a distance of a few centimetres, the parietal peritoneum and the fibrous connective tissue of the muscles are dissected (an easy enough matter because of the state of imbibition and atrophy of the wall), and are then removed. 3. The whole surface of the epiploon, which is often cirrhotic, distended, and enlarged, is fixed at its lower portion for 2 or 3 cm., according to the case, beneath the old umbilical cicatrix; on the side, as far away as possible from the median incision, it is fixed to the abdominal wall with silk sutures passed through its whole thickness, the peritoneum having previously been scraped with a blunt spoon and with wads of sterile gauze. 4. The epiploon having been fixed, the margins of the incision are sutured, the subjacent epiploon being drawn up into the suture line, especially at the seat of the umbilicus, so that the epiploon, firmly fixed in the centre, laterally, and below, comes in direct contact with all the muscular tract of the abdominal wall, which has already been denuded on each side of the wound, especially at the site of the umbilicus, which it replaces. The suture consists of two silk layers—a deep one with separate stitches and movable loop, and a superficial one. As a rule, the deep stitches can be removed on the fifth day, and the superficial ones on the seventh or eighth. The advantages of the operation are:

1. That our hopes of the development of anastomoses do not rest merely upon the adhesion of a small portion of the epiploon to the wound, but upon that of nearly the whole surface of the epiploon, which is of great extent.

2. That the adhesions are extensive and richly vascular throughout the large portion of the abdominal wall, in which there is direct contact of the epiploon with the submuscular tissue.

3. That the development of a collateral circulation is greatest at the site of the former umbilicus, because it is favored by the complete removal of the cicatrix, and by the direct manner in which the epi-

ploon is placed in contact with the cutaneous venous branches of the various groups of accessory portal veins.

Schiassi, of Bologna, also proposed the intramuscular insertion of the epiploon, and he performed it on three patients according to his process, which consists in a longitudinal incision with a second one transverse to it under the costal arch and through all the tissues; the epiploon is drawn out and spread out under the triangular flap, the parietal peritoneum having first been detached from the muscles; the sutures are inserted in layers. This process is more complicated than the others and does not appear to possess any special advantages.

Surgical intervention in cirrhosis has not a few adherents and Van der Meulen, Schelkly, Lens, Morrison, Weir, Raimod, Comandini, Salvolini, Solokoff, Raffa, Schiassi, Clementi, Carle, and Pascal have published the reports of 40 cases. Of these, 2 patients died from the operation; 1 from consecutive septicæmia; 11 were not improved; 7 had merely temporary improvement, as death occurred in from one to eleven months after the operation; 4 were considered cured, because the ascites had not returned after from twelve to fourteen months; and finally, in 5 cases the time which had elapsed since the operation was too short to allow of a definite opinion as to the results.

In certain patients who had been operated on and in whom the formation of a collateral circulation was quickly attained, Morrison and Pascale noticed that the dropsy disappeared; but there was a period of strange nervous excitement and of disconnectedness in ideas, while the patients gradually fell into a state of depression until they became comatose, and after an alternation of these different symptoms death followed with rapidity. In the case of one of Morrison's patients the comatose state could be overcome by energetic intestinal derivation, and finally a complete recovery ensued. The explanation of this circumstance seems to be that there was a condition of general toxæmia, resulting from the fact that blood from the intestines went into the general circulation without going through the parenchyma of the liver, and, therefore, without being subjected to the antitoxic action of that organ.

What value are we to attribute to surgical measures in ordinary cirrhosis, in view of the results of clinical experience and experimental research?

Very certainly ascites is merely a symptom of the disease, although the most prominent and the most important one, hence we cannot speak of etiology in the true sense of the word, nor of treatment of a morbid process. On the other hand, it is well known that by curing the symptom of a disease we may give the disease time to exhaust itself, and may remove a cause of death. Talma's operation, in our opinion, may postpone the fatal ending of the disease, but it cannot

be considered a true and rational treatment of the cirrhotic process, which, unless arrested by other means, will go on to its lethal termination. Up to a certain point the improvement of the collateral circulation by the diminished vascular irrigation of the liver will decrease the physiological work demanded of the hepatic cell, and thus bring about a condition of functional rest—a condition that can also be attained by a milk diet. Nor should we underestimate the fact that by means of laparotomy we often have marked improvement of the perihepatitis and the chronic peritonitis which so frequently accompany cirrhosis. But Talma's operation does not in the least overcome the hepatic insufficiency to which death is due in many cases of cirrhosis.

Therefore, as a practical conclusion, we may say that, all things considered, surgical intervention deserves a place in the treatment of hepatic cirrhosis because of its useful results. Such an operation should, of course, be reinforced by medical treatment, and especially by a rigorous milk diet, which secures a reduction to the minimum of the toxic products normally formed in the intestines. But we are not to expect from operation a real cure of the cirrhosis, for the hepatic insufficiency remains always as an imminent source of peril.

Acute Yellow Atrophy.

The etiology of this grave hepatic lesion is still obscure, but it has always and increasingly attracted the attention of pathologists, who are endeavoring to find the pathogenic agent.

The bacteriological results obtained by a number of investigators have already succeeded in discrediting the idea of a single pathogenesis, which is no longer accepted by the majority of practitioners, who are inclined either to believe in a general multiple infection, or to hold that there is an autotoxic genesis. Because of the predominance of the diffuse and marked general disturbances in this affection, other pathologists place it in the class of acute general infective diseases with primary localization in the kidneys, and secondary in the liver. This latter view appears to be confirmed by results obtained by Baimakow in a case of acute yellow atrophy of the liver in a man of twenty-three years. In the blood extracted during life and stained by a special method (a half-hour staining with a mixture of yellow eosin and methyl blue), a special diplococcus stained a dark blue was found, which bore much resemblance to Fraenkel's pneumococcus, but differed from it in being stained by this method. This would appear to be a new species of microorganism, which increases the number of those capable of causing acute yellow atrophy of the liver.

In addition to the coli bacillus, the streptococcus, the staphylococcus, etc., regarded as the cause of grave icterus, Bar and Rénon found

in a new-born child the *Proteus vulgaris* in the contents of the umbilical vein and the heart, and in the substance of the liver and spleen. In this case the point of entrance was the umbilical vein, which was affected with phlebitis. It would seem to be the case that acute yellow atrophy is of multiple origin, and it is probably a general infective disease, with its chief localization in the liver.

From exact uranalysis Setti reached the following conclusions: The total elimination of chlorides, sulphuric acid, urea, and ammonia is much diminished, even taking the alimentation into consideration. The elimination of uric acid is normal taken by itself, but considering the nature of the food, it is increased. The total acidity of the urine is increased, and the amount of nitrogenous extractives enormously so. The ratio between chlorides and urea and between alkaline and earthy phosphates is normal. That between the combined and the preformed sulphuric acid is low, and that between uric acid and urea is reduced to a minimum and in favor of the uric acid. The relation between ureal nitrogen and the total nitrogen is low, the former being greatly diminished in relation to the latter. With the increased acidity of the urine we find a good amount of acetoacetic acid, and this testifies to acid intoxication of the organism, which must be taken into account in the interpretation of the coma in these patients. In addition to this acid, the other pathological elements found in the urine are albumin, bile pigments, and traces of bile acids.

The Surgical Treatment of Hepatic Tumors.

Nosenthal has reported the successful removal of a malignant tumor from the lobe of Spigelius in a woman of forty-one years by placing an elastic ligature on the organ 2 cm. below the insertion of the tumor. In 1898 M. Robson reported that out of three hundred cases of hepatic disease, of which thirty-six were of malignant neoplasms, in three cases only did he find it possible to remove a small portion of the liver, of the gall bladder, and of the cystic duct. In two of these recovery ensued, while the third patient died from a return of the tumor.

Robson holds that, as hepatic calculus is often complicated by carcinoma, prompt surgical intervention is to be recommended in cholelithiasis, which procedure will, if systematically followed, greatly reduce the number of cases of cancer of the liver and of the gall bladder.

The clinical and experimental researches which have been made give us ground to hope that the removal of hepatic tumors with resection of the glandular parenchyma will before long take its place in practical surgery as an approved procedure.

HERNIA.

BY

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THERE has been a marked advance in the past few years in the operative methods for the radical cure of certain varieties of hernia, especially inguinal and femoral. We agree with Blake in his demonstration that the old method of cutting the fibres of the internal oblique is unnecessary. It is, besides, very apt to weaken the canal, and is being gradually given up. A great deal of work has been done on cadavers to make this point clear. Much confusion has arisen from the wrong application of the term "conjoined tendon." Blake has recently reported the results of the dissections of twenty-five subjects of fine muscular development. He says: "As a rule the lowermost fibres of the internal oblique do not enter into the formation of the conjoined tendon, but, arising from Poupart's ligament, in front of the cord, pass parallel with the ligament to be inserted in front of the rectus. If the internal oblique be reflected, the conjoined tendon is found to be chiefly derived from the deeper aspect of the internal oblique, and slightly from the transversalis where these muscles are inseparably connected at their origin. It consists mainly of a few scattered muscular fasciculi arching over the cord, to be inserted to the iliopectineal line. The conjoined tendon is thus covered by the lower part of the internal oblique muscle, and it also lies in front of the main aponeurosis of the transversalis, for the fibres of the latter are easily demonstrated as passing behind the conjoined tendon to unite with the internal oblique in front of the rectus. This relation is usually overlooked on account of the tenuity of the transversalis aponeurosis in this region." In the dissections of this writer in not one case was the conjoined tendon inserted more than five-eighths of an inch laterally to the insertion of the rectus muscle. In the greater part of these cases the distance was less than one-half inch, and in some it could not be distinguished from the insertion of the internal oblique. In every case it consisted of only scattered fibres, either muscular or tendinous. But the thickened transversalis fascia formed a definite posterior wall

to the inguinal canal. Blake believes that the essential factor in the cure of inguinal hernia is in the restoration of the normal direction of the fibres of the internal oblique, *i.e.*, parallel to Poupart's ligament. The crying objection, according to this author, to Halsted's method of cutting the internal oblique is the lateral division of the nerves. He says: "Our main reliance in radical cure is the internal oblique, and our efforts should be to restore the normal parallelism of its fibres to Poupart's ligament. This may be done in nearly all cases by separating the internal oblique for a short distance upward from the transversalis fascia and the transversalis aponeurosis, and then, thus having loosened it, it may be drawn down by the sutures to Poupart's ligament. As a rule, it is futile to attempt to draw down the transversalis aponeurosis, since this structure is normally deficient for a considerable distance above the ligament."

Ochsner discusses the features determining the permanency of cure in the radical operation for inguinal hernia. The essential points to be observed are: 1. The wound must heal primarily because suppuration results in an abundance of cicatricial tissue, and this is most unstable. 2. The stitches must not be drawn tightly in order to avoid pressure necrosis. 3. The edges of the wound to be united must be free from fat and other unstable tissues. 4. The wound should be supported by broad rubber adhesive plaster strips until healed. 5. The patient should be kept in bed from two to three weeks. 6. After the operation abnormal intraabdominal pressure should be eliminated by avoiding constipation, etc. In inguinal hernia: 1. The entire sac should be removed. 2. It is especially important to remove all the loose tissue between the transversalis and internal oblique muscle on one side and Poupart's ligament on the other. 3. The upper part of this canal should be closed with especial care. 4. A long, thin omentum, if present, should be resected. Thornton Parker reports a case of double inguinal hernia, with a serious prolapse of the rectum, due to an equestrian accident.

In operation on the inguinal, Whiteford suggests that if there is any question as to whether the bladder has been opened, the way to prove the point is to test with litmus the liquid which flows out. If the reaction is acid, it needs no further proof that the fluid is urine. According to this writer, the acid reaction of cyst contents in the inguinal region is found only in the case of urine.

Service Hernia.—Robinson gives his experience with hernia among our troops in the Orient. Excepting gunshot wounds, hernia is the most common surgical condition in the Philippines. This is due to various causes: to the general loss of muscular tone, the extreme and sudden loss of flesh, the great strain of the life, but especially to the army belt. The use of this has been abandoned in almost every army

but our own. The writer reports his own cases, 53 in number; of these 45 were inguinal, 6 were ventral, and 2 were femoral. In the tropics shock in operation is common, and chloroform is badly borne. Recurrence, however, is rare. Ventral hernia is not so favorable for treatment, and it is questionable if operation is justifiable. But in every case of inguinal and femoral hernia radical operation is indicated.

In John Langton's statistics, in a total of 7,661 cases of ruptured males, 4,310 were ruptured on the right side, 2,812 were on the left, and 539 were double. In 174 cases the testes were misplaced. The largest number of inguinal herniæ in both sexes occurs between the ages of 15 and 25. Hernia into the tunica vaginalis testis, between the ages of 16 and 25, occurs a little oftener on the right side than on the left.

Warren reports 98 cases of operation for hernia, 58 of which were carefully traced. In 84 per cent. of the inguinal herniæ there was no recurrence one year or more after operation. The improvement in the results is due to asepsis and change of technique. Recurrence is more frequent in umbilical hernia than in the other varieties. The cures following operation for inguinal hernia before 1895 amounted to 69 per cent.; since 1895, to 92 per cent. Warner advises as early operation as possible in umbilical hernia on account of the tendency to suppuration and recurrence in this variety. Barker warns against the too tight suture, for this gives rise to necrosis, and thus offers a nidus for pus organisms.

Inguinal Hernia Associated with Descent of the Testis.—John Langton gives some interesting statistics: He states that the descent of the testis is a process in development, which exerts a powerful influence as an etiological factor in hernia in infants. As age advances, it becomes less potent in the causation of hernia. The weakness due to the passage of the testis remains, to a certain extent, throughout adult life, and is always a predisposing factor in the causation of hernia. The fact that the processus vaginalis is frequently unclosed to a greater or less extent at birth without any extrusion indicates that hernia does not depend entirely upon the patency of this process. He also emphasizes the fact that the existence of the vaginal process does not seem to depend upon the descent of the testis, since the testis may be retained while this peritoneal process lies complete in the scrotum and entirely "shut off from the general abdominal peritoneal cavity." Further observation demonstrates the correctness of Langton's conclusions that the non-descent of the testis is the predisposing cause of a large number of herniæ, especially in cases of the congenital variety. His statistics, showing that hernia is far more frequent in infancy than in later life, inguinal hernia being eleven times more

frequent in males than in females under twelve months, 3,215 boys to 290 girls, and in these boys three times more common on the right side than on the left, while in girls it is nearly equal on the two sides, prove a direct relation between the passage of the testicle and weakness of the abdominal walls and the failure of the tunica vaginalis to be shut off at the internal ring. Another point to be noted is that under normal conditions the right testis does not descend as early as the left, so the processus vaginalis on the right side remains patent to a later period than that on the left, thus preventing the closure of the right internal ring, which acts as a predisposing cause of hernia on the right side. Premature children are very liable to hernia at birth, and in them it occurs more often on both sides than it does at full term. In the case of malposed testes, the greater number are on the right, the proportion being 92 on the right to 57 on the left, out of a total of 149, that is, as 6 to 4. In nearly all cases the testicle is small and ill-developed. It is generally soft and flattened, and is more tender and sensitive than normal. Langton does not believe that retained testes are apt to become malignant. As to the different positions in which the malposed testes are found, the two most frequent situations are in the inguinal canal, and at or near the mouth of the external abdominal ring. The testes are small, and they are more frequent on the right side than on the left.

In discussing interstitial hernia, Langton states that the most frequent position of the testes in this variety of hernia is on the right side in the inguinal canal. The proportion of interstitial herniæ, in a total of nearly 50,000 cases, was found to be 1 to 1,100 cases. Out of 13,583 female patients, there were 18 cases of interstitial hernia, that is, 1 to 760. Operation is difficult in this form of hernia, for the separation of the muscles makes approximation of their edges practically impossible. The hernia is so large that the abdomen cannot accommodate the mass of reduced intestines, and the problem of performing an enterectomy has to be considered.

Eccles reports two cases which show the variations in inguinal hernia, due to abnormal descent of the testis. The first patient was a man aged twenty-three, with interstitial hernia. Neither testis was wholly descended. The right was in the canal, while the left was near the deep abdominal ring. The sac of the hernia was probably between the aponeurosis of the external oblique and the internal oblique muscle. It is almost without question that the abnormal descent of the testis was a factor in the causation of this interstitial hernia, but it cannot be the only one, since this variety of hernia is found also in women. The smallness or absence of the superficial abdominal ring may be quite influential in causing the hernia to pass the plane of least resistance. The second case was one in which the sac followed

the course of a badly formed testis. It had not entered by the normal route into the scrotum proper, but had distended the skin at the point of junction of the thigh and scrotum. The right testis was in the perineum, and was under the normal size, and tender. The sac was covered with ordinary skin and contained no dartous tissue.

Foreign Bodies in the Sac.—Various interesting reports of this nature have been made. Williams, in a post-mortem examination of a case of irreducible hernia of long standing, discovered a small yellow body about the size of a pea, cartilaginous in structure. It was loose in the sac. Another similar object was found in the same case in a vein of the sac wall. This was about two inches above the testicle, and was in the process of ulcerating through the venous wall. He regarded these bodies as fibrous phleboliths, and thought that their origin was a blood clot, following an old inflammation in the valve of a vein. The clot organized later and became fibrous.

Milligan reports the case of a calcified lipoma which was found in a hernial sac. This probably came from an appendix epiploica. Morf reports an interesting case in which there was a hernia of the Fallopian tube alone without the ovary. He believes that this patient had a congenital hernia of the left oviduct which was complicated by epiplocele. The fatty part of the latter underwent serous change. At examination the hernia was irreducible. This, Morf accounts for as follows: The patient was probably attacked by acute vaginitis. The infection extended upward and involved the omentum, causing exudation and pus formation. The increase in size caused the hernia to become irreducible. In another case of irreducible inguinal hernia in a woman thirty years of age, Shufelt found in the sac a perfectly developed tube and ovary.

Göschel declares that a diagnosis between incarceration and perityphlitis in a hernial sac cannot be made previous to operation. This is not a disadvantage, however, as operation is indicated in either case. He reports a case of this kind in which he resected the cæcum and vermiform appendix. Tenny reports a case of appendicitis in a femoral hernial sac. The patient was a woman of seventy-nine years. The hernia was below Poupart's ligament and was tender and doughy in consistence. On opening it, a little pus and scybala were evacuated. Embedded in fat, with a pedicle which extended back to the femoral ring, was the appendix. It was adherent to the ring. It was tied off close to this point. Hernia of the vermiform appendix alone is rare. Bajardi collected from the literature in 1895 fifty-seven cases of inguinal, forty cases of femoral, and one case of obturator hernia. In cases of this kind there are the same symptoms as in ordinary appendicitis, only local tenderness is the most striking symptom.

Larimore reports a case of hernia of the ovary and tube and

vermiform appendix in a woman thirty-five years of age. There was a left oblique inguinal hernia, irregular and doughy, the size of a small orange, and irreducible. The patient had had trouble on that side in childhood. For the last fifteen years the lump had been increasing in size and had been growing more painful.

We indorse Ochsner's conclusions in relation to the treatment of hernia in children that a large number of herniæ in children can be cured by the continued wearing of a suitably applied truss. Ochsner believes that these children can be cured also by keeping them in bed with the foot elevated for a period of six weeks, but probably a large number can be cured only by operation.

Hernial Tuberculosis.—G. Chavannaz reports a case of right inguinal hernia, with ectopic inguinal testicle, and tuberculosis of the sac and hernial omentum. The hernia was sometimes a little painful. When the sac was opened, a quantity of serous liquid flowed out. The hernial omentum was resected, and microscopical examination showed typical tubercles. Radical operation was followed by cure. Hernial tuberculosis is rare. It may manifest itself at any age, but is more common in the young, and especially in children. The prognosis is relatively favorable if the disease has not yet invaded the intestine.

Injection Treatment.—Although experience has proved this method to be unscientific, its advocates still appear from time to time. Holmes speaks of two solutions of which he makes use. The principal constituents of these are zinc sulphate, creosote, and cocaine hydrochlorate. The technique, as described by this writer, is as follows: After locating the outer margin of the internal ring by invaginating the scrotum, from six to ten drops are injected. Before the patient rises a truss is applied. This is repeated in two days on the opposite side of the ring. Again, three days later, the injection is repeated half-way down the canal, on the side of Poupart's ligament. Other treatments may be necessary. The results of the injection treatment have proved too hazardous to warrant further experiment with it.

Radical Cure of Femoral Hernia.—Two new methods seem worthy of mention. They are those of Battle and Gordon. Battle's method consists in bringing down a part of the aponeurosis of the external oblique muscle, and using it as a shutter to cover the upper part of the femoral canal. It is sutured to the fascia over the pectineus muscle and to Gimbernat's ligament. Extra sutures are added to secure the displaced aponeurosis in its altered position. Gordon's method aims to bring down portions of fibres of the transversalis and internal oblique and unite them to the pectineus muscle, the object being to press down the fibres of the muscle against the femoral opening. The sac is treated somewhat according to Kocher's method. Ochsner believes that in femoral hernia the canal through which the

sac protrudes is a perfect ring, and consequently, if the entire sac is removed, this ring will invariably close, and there can be no recurrence. All meddlesome operations contemplating the closure of this ring cause a certain percentage of recurrences. Delbet states that in the Service des Bandages of 1,586 patients with hernia, 70 only were femoral, and 2 of these had recurred after operation.

Sliding Hernia of the Cæcum and Sigmoid Flexure.—Weir believes that this condition, "Hernie par glissement," is due to a defective investment of the cæcum or ascending colon by peritoneum. Owing to this, the hernial sac is not complete. The nature of this hernia is difficult to discover before operation. According to Weir, this is rather a common condition, and is more frequent on the left side, and in males of middle age or advanced life. It is reducible when recent, but soon becomes irreducible, and, as a rule, is scrotal. Not every case of cæcal or sigmoid hernia is of this nature. Weir quotes Treigney's statistics: Of herniæ of the cæcum and appendix, there are 8 inguinal and 5 crural; of the cæcum and end of the ileum, there are 11 inguinal and no crural; of the appendix alone, there are 17 inguinal and 5 crural; of the transverse colon, there are 45 inguinal and no crural. Of herniæ containing the cæcum, end of the ileum, and ascending colon, there are 8 inguinal and 1 crural; of those containing the sigmoid flexure, there are 14 inguinal and 1 crural; of those containing the sigmoid flexure with the small intestine, there are 7 inguinal and no crural; of those containing the ascending or descending colon, there are 5 inguinal and no crural.

Froelich has gathered some 21 cases, 10 strangulated, and 11 in which a radical cure was attempted "à froid." There were 6 cæcal herniæ, 4 strangulated sigmoid herniæ, and 9 non-strangulated.

Umbilical Hernia.—The new method advocated by Blake is almost identical with that described by Mayo, Sapiejko and Piccoli. A median incision is made down to the aponeurosis of the recti; the sac is isolated and the hernial contents are reduced. The sac is then clamped at its base and the protruding part excised. Both of the recti are separated from the overlying fat for several inches, and the edges are then overlapped, the posterior surface of the left muscle being sutured to the anterior surface of the right, and vice versa. The margin of the rectus, which underlaps, is attached by mattress sutures, which pierce its edge and the opposite rectus; the rectus which overlaps is sutured to the anterior sheath of the opposite rectus by the interrupted suture. Blake believes this method best adapted to herniæ in which there is separation of the recti. It may also be used in cases of enteroptosis with lax abdomen. By this method the abdominal wall is doubled at the hernial site; the lines of suture are broken; there is obliteration of the separation of the recti; the size of the abdomen is

lessened, and the surfaces to be united are broad. The union of such broad surfaces makes future separation improbable. Piccoli has experimented on dogs, and has found that from two weeks to four months after operation the union, even under the microscope, is very firm. He reports satisfactory results.

Ochsner reports an ingenious method, first described by Mayo, by which the edges of the hernial ring are overlapped either from above downward or from side to side for one and one-half inches. This method has also been worked out by Blake. The results are so far most satisfactory. Hemsted reports an unusual case of umbilical hernia, in which there was extrusion of the intestines, and finally rupture of the hernia, with no sloughing of the hernial sac.

Several notable cases of hernia into the umbilical cord have been reported within the last few years. Two of these were Kennedy's patients. One was a boy twelve hours old when operated on. The cæcum, appendix, and several inches of both large and small intestine were found in the sac. Recovery took place with no bad symptoms. The second infant was operated on when only one hour old, and did quite well.

Vesical Hernia.—An interesting case of vesical hernia in a child is described by Adams. There were no vesical symptoms. The hernia was reducible and had no connection with the testicle. In opening what was supposed to be the sac it was found to be a diverticulum of the bladder. This bit of the bladder, which formed the hernia, was closely adherent to the cord and canal. The bladder protruded into the canal at the internal ring. There was no sac. After the diverticulum was excised, the bladder opening was sutured. A silkworm-gut drain was inserted for four days, but the wound healed at once.

Another case of vesical hernia is described by Harrington. The bladder in this instance protruded through the pelvic outlet, dragged down by a large subperitoneal fibroma. The fibres of the levator ani had been separated by the tumor in its growth. The bladder had penetrated through an opening in the levator muscle fibres, and complete retention of urine resulted. Abdominal incision was made, but it was not possible to remove the tumor and restore the bladder, and so both tumor and bladder were approached through an incision from the ischial tuberosity to the upper end of the labium. The bladder and tumor were distinguished with difficulty, and the former had to be distended with air to make their separation clear. The tumor was then removed and the bladder restored to its normal position. On account of the marked tendency of the bladder to escape again through the muscular opening, the uterus was employed to close the opening. As the patient was forty-six years old and had suffered from repeated uterine hemorrhages, this was considered legitimate. The appendages

were first removed. The recovery was complete, and there has been no recurrence of bladder symptoms since the operation.

Inguinal cystocele is more frequent than crural. Moynihan gives the following statistics: Among 2,543 operations there were 23 bladder herniæ. These cases were those of the following operators: Lucas-Championnière, Krönlein, Bassini, Habs, Corazza, Morrari (Novaro's cases), Montegnacco, and von Hacker. This would be roughly one per cent. of cystocele. In general, cystocele is a disease of the aged and feeble. Four cases only of inguinal cystocele in children have been recorded. The average age of males with this affection is 51 years: of females, 44 years. The majority of cases occur between 50 and 60 years. The relative frequency of the occurrence on the right and left sides is as 1.46 to 1.

Ansinn, in a recent pamphlet, records 33 cases of crural cystocele, 30 of which were in women. The part played by the prostate is probably similar to that of pregnancy and its attendant conditions in women. Of these cases, 20 were extraperitoneal, 8 paraperitoneal, and 1 intraperitoneal. Only 3 patients had symptoms which made the diagnosis positive.

Treatment of Ventral Hernia Following Cœliotomy. — Gottschalk, Clark, and Eads have made valuable contributions to this subject which has attracted so much attention in the last decade both in Europe and in this country. Any oblique incision crossing the linea alba is to be avoided, from the resulting tendency to ventral hernia. Gottschalk believes that it makes no difference whether the incision is made exactly in the linea alba, or a little to the side in the aponeurosis of the rectus. A valuable point in this operator's technique is his avoidance of superficial dead spaces in the wound by catching the underlying aponeurosis with its superficial fascia. He also clamps the skin and peritoneum together and so eliminates the chance of contaminating the muscles and fat. He closes the abdominal wound with two layers of silk sutures. A most important point in the operation is the accurate approximation of the edges of the aponeurosis. This is even more important than the approximation of the muscle fibres, for there is slight adhesion between the long muscle bundles, as may be proved by the gentlest manipulation. According to Clark, the success of the operation depends upon the proper observance of this detail. Gottschalk does not use a pad in cases of post-operative herniæ for fear of causing adhesions of the intestine or omentum to the sac. In operating on such cases, Maydl, after opening the sac, removes the redundant part of the skin and peritoneum, and, after freshening the aponeurotic edges, closes the wound by through-and-through interrupted sutures. That part of the omentum which is adherent should be excised because of its cicatricial tissue, which may give rise to in-

flammation, and if returned to the abdomen, result in new adhesions. At the end of the operation adhesive plaster is snugly applied over the wound to prevent tension of the sutures.

Eads lays great stress on the importance of leaving as intact as possible the nerve supply of the muscles concerned in the operation. When the muscle is enervated, its value as a protection is gone and hernia is most apt to result. He believes that as high as fifteen per cent. of cœliotomy cases develop hernia within five years after operation. When the nerve of a muscle is destroyed, not only is its contractility lessened, but also its blood supply. With this fact in view, he makes all incisions, as far as possible, either parallel with or in the direction of the nerves of the region. As to the incision, he advocates the long one through the skin and superficial fascia, in that it shortens the operative procedure. In this connection it is appropriate to mention McBurney's intermuscular incision. Statistics show that this method is followed by fewer herniæ than the older ones. Our experience at the Hospital for Ruptured and Crippled has demonstrated to our own satisfaction the superiority of closing the abdominal wound in layers by the use of absorbable chromicized catgut or kangaroo tendon.

Buck gives a communication along these lines. He shows that division of aponeurosis is bad without supporting muscle. Ventral hernia is frequent after such operations. Even when the muscle is divided in the direction of its fibres, the result cannot be satisfactory if at the same time its motor nerve fibres are divided, and if the incision is not supported by uninjured muscle or aponeurosis. He enumerates the following steps: 1. Incision through the skin, superficial fascia, and fat. 2. Division of sheath (anterior). 3. Enucleation of muscle from its sheath outward. 4. Division of sheath (posterior), together with transversalis fascia, subperitoneal fat, and peritoneum. 6. Suture of sheath (anterior). 7. Suture of skin and fat. The advantages of this operation are: Extreme simplicity; division of aponeurotic structure only, such being afterward supported by a strong muscle entirely free from injury by sutures or division of nerves; extreme improbability of hernia; great reduction in time of the period at present necessary for convalescence after simple cases of laparotomy; the rectus is uninjured and is a protector.

Schenk reports a very interesting case of congenital, lateral, ventral hernia in an infant after a breech presentation. The hernia was on the right side between the ribs and crest of the ilium, and was the size of a walnut. It was greatly increased by hiccough; examination revealed no congenital lack of development. And the writer attributes the hernial opening, which was two-fifths of an inch in diameter, to the pressure of the strongly flexed knee during birth, as the knee fitted snugly into the gap in the muscles.

Johnson describes an improved method of operation for ventral hernia which is really much like the old quill method. Silver wire sutures are passed through the peritoneum, rectus muscle, and skin at intervals of one inch through the entire incision. After the subcutaneous tissues are united by continuous suture of kangaroo tendon, the deep sutures are taken up one after the other by winding the wire around an ivory pencil on either side, and are drawn tight enough to relieve the tension on the kangaroo sutures.

Hammesfahr reports very successful immediate results in large ventral herniæ complicated by separation of the recti, from the following method of operation; it is yet too soon to report permanent results: He first removes as wide a strip of skin with the underlying fat as possible, reaching from the symphysis pubis to the ensiform process. The hernia is reduced without opening the sac. The sheath of the rectus is opened from end to end and the muscle bellies are freed. Sutures of silver wire, or aluminum bronze, are passed through the anterior sheath of the rectus and the muscle near its lateral limit; they are then passed between the posterior sheath and the belly of the muscle toward the median line, and finally forward through the muscle and sheath. They now cross the median line one by one in the reverse order, to come out at the lateral border of the sheath of the rectus. When the sutures are tied, the bellies of the muscles are approximated, folded a little inward with the anterior sheath between them. The skin sutures close the operation.

Ochsner states that in ventral hernia following laparotomy the original layers should be laid bare, and that the corresponding layers should be carefully united. He prefers deep silkworm-gut sutures, to be tied after each layer has been united separately with chromicized catgut sutures. It is important to wear an abdominal binder for several months after laparotomy.

Diaphragmatic Hernia.—An interesting case of diaphragmatic hernia has recently been reported by W. Moser. The greater number of these herniæ are caused by traumatism, and, as a rule, are fatal. There is another class in which the hernia is congenital, and is associated with malformation or malposition of different organs. The heart is not infrequently found on the right side in both congenital and traumatic cases. In Moser's case the hernia formed a large mass in the epigastric region. The patient had suffered from this hernia for some years and made the statement that it had appeared simultaneously with a double inguinal hernia. He knew of no cause for it. He declared that he did not have it as a child. The mass was easily replaced. It probably contained a part of the stomach and intestines. The point that distinguishes this hernia as a diaphragmatic hernia, and not purely epigastric, is that after reduction, several fingers could

be passed through a large opening in the diaphragm, and the heart could be seized with the fingers. This case bears evidence to the fact that not all acquired diaphragmatic herniæ are due to severe traumatism, nor are they necessarily fatal. The writer thinks that it is probable that cases of this nature are due to a slight injury, or to heavy lifting, and that an opening or malformation which is congenital and easily dilatable preëxists. In an interesting case, reported by Abt, the greater part of the stomach and the small intestine were in the left thoracic cavity.

Intestinal Obstruction due to Hernia of the Transverse Colon into the Foramen of Winslow.—We are indebted to Groves for the report of the following case: The patient was a woman of forty-seven years, suffering from symptoms of intestinal obstruction—borborygmi, distention, etc. The external signs stopped abruptly to the right of the median line below the liver, where there was tenderness. The abdomen was opened, and a dark-red liquid flowed out. The cæcum and ascending colon were greatly distended, while the sigmoid flexure and descending colon were empty. The obstruction was discovered to be due to the passage of the transverse colon under the liver and under a band which formed the anterior wall of the foramen of Winslow in which the hepatic artery was pulsating. The intestine was withdrawn without difficulty and double enterotomy was performed. An artificial anus was made for a safety valve in case of the recurrence of the obstruction, which, indeed, took place.

Epigastric Herniæ and Fatty Tumors in the Epigastrium.—Lothrop states that these may be due to embryonic defect, to injury, to weakness in the abdominal walls, and, besides, there is evidence of the influence of properitoneal fat and terminal vessels and nerves as etiological factors. Epigastric herniæ and fatty tumors are, as a rule, of slow growth. They have a tendency to develop at that point where the vessels pass forward through the anterior sheath of the rectus muscle, especially in the linea alba. There are often gastrointestinal disturbances, with or without local pain, although in some instances there is nothing abnormal to be noticed. It should be remembered that lipomata may be mistaken for epigastric or femoral herniæ.

Incarcerated Hernia.—Frederick A. Packard suggests an ingenious explanation for the cause of meteorism and partial intestinal obstruction. It is that a loop of intestine is formed so that it acts like a trap similar to that used by plumbers to prevent the entrance of sewer gas through the drain-pipes. This arrangement will permit of the overflow of fluid material which would absolutely prevent the escape of gas, unless the peristaltic force were sufficient to force the fluid out of one arm of the U. Such a condition could follow any inflammatory lesion of the lower abdomen. There might be no symptoms until the

walls of the intestines were so weakened that the resistance of the contents of the limbs was great enough to cause an accumulation. It might follow the liberation of an incarcerated hernia. Rodman found such a loop at autopsy in a fatal case of relieved incarcerated hernia.

Marcy reports two fatal cases of incarcerated hernia. A most important question to be considered is the danger to life, due to increase of intraabdominal pressure. In cases in which any large part of the abdominal contents has been for some time displaced, Marcy advises keeping the patient in bed for quite a while with limited diet and moderate purgation. By this treatment the mass of displaced intestines is reduced to a great degree, and the abdominal wall will be relaxed and thinned to a still greater degree. This fact has a most important bearing on old, very large, retained herniæ, which are to undergo surgical treatment. The case, so treated, may nearly always be cured.

Treatment of Intestinal Obstruction Caused by Incarcerated Hernia.—Wright urges promptness in these cases, to restore the suspended function of the tissues. When strangulated hernia is diagnosed, the bowel must be released. Often taxis with anæsthesia is successful. A full hypodermic of morphine before the anæsthetic is very beneficial. Great discrimination is necessary in using taxis. It is a safe plan to decide on operation before the necessity for it is absolute. Wright believes that the greater number of cases can be safely relieved by early operation but that delay is always fatal.

Causes of Death in Strangulated Hernia.—Jones sums up this subject in a very satisfactory manner. In cases of resection, especially, there is always a possibility of failure of anastomosis, as well as that of shock and sepsis. Without operation the cause of death is generally shock. With or without operation there is always danger of general peritonitis. This may result from extension of the infection from the hernial sac, from escape of fæces, necrotic ulcers of the intestine at a distance from the hernia, caused by asphyxia of the intestine, sloughing of the intestine, paralysis of the intestine without sloughing, causing sometimes fatal hemorrhages, septic peritonitis, general septicæmia, ileus, etc. No case is safe until we are assured of the restoration of bowel function. In operation there is danger of accidental injury to the intestine, infection of the peritoneum, intestinal obstruction from post-operative adhesions, hemorrhage, shock, accidents from anæsthesia, artificial anus, and operation for its closure, and failure of anastomosis.

Extensive Resection of the Small Intestine in Strangulated Hernia.—An interesting case of this kind is reported by Lauwers, who considers the resection of anything over two metres (78¾ inches) of the small intestine an extensive resection. The present case was that of a rachitic woman of sixty-five years. At the age of thirty-five this patient

had given birth to a child, but on account of the deformed pelvis it was necessary to perform Cæsarean section. This operation was followed by the development of a large umbilical hernia in the scar. When the patient was seen by Lauwers, the hernia had been strangulated for three days, and had resulted in a fæcal fistula, from which large quantities of yellow fluid were flowing out over the skin, which was much irritated and excoriated. The hernial sac was opened. It contained closely adherent loops of small intestine. It was found to be impossible to separate these adhesions, and so the entire hernial mass was excised and end-to-end anastomosis performed. The patient made a good recovery. The removed intestine measured 265 cm. (104⅓ inches). On the eighth day solid nourishment was given, which caused diarrhœa and indigestion. These disturbances, however, quickly subsided. The mortality in these resections has been quoted at 16.6 per cent. Lauwers believes that the prognosis depends more upon the gravity of the lesion than upon the length of intestine resected—up to certain limits.

In a case of Juillard's a part of the large intestine adhered so closely to the hernial sac that he resected about eighteen inches, and also performed castration. He then did a circular enterorrhaphy. After ligaturing the sac, he replaced it in the abdominal cavity, and sutured the pillars of the internal ring. The wound was then closed. Complete recovery followed.

Strangulated Hernia in Infants.—Erdmann reports the case of a child thirteen days old suffering from an irreducible, strangulated, inguinal hernia. He relieved the strangulation and performed a radical cure at the same time. The recovery was rapid and uneventful, the wound healing by primary union. Lilienthal operated upon a strangulated hernia in a child of eight days. In this case the ascending colon, sigmoid flexure, and appendix, together with a large part of the small intestine were involved. After the canal had been slit up, the hernia was with difficulty reduced. The wound was practically healed within six days after operation. Dowd says that infants endure this operation very well. The symptoms in the order of their relative importance are: tumor, vomiting, constipation, difficulty in urination, restlessness, apparent pain, and constitutional depression.

Guinard and Vernon report the case of a premature infant of eight and one-half months, taken from couveuse two days after birth and operated upon for strangulated umbilical hernia. Strangulation is a gradual process in infants.

D'Arcy Power reports a case of strangulated hernia in a premature child of five weeks. The child recovered from the operation. Although strangulated hernia in young infants is very rare, still the mortality in those cases in which operation is performed is not high.

Nearly one-half of the cases of strangulated hernia in children under one year occur during the first three months. According to Newbolt, in cases of strangulated femoral hernia, in which the intestine is resected, the Murphy button has given good satisfaction. An artificial anus is the alternative.

Hemsted reports an unusual case in which the vermiform appendix formed a femoral hernia. The patient was a woman of thirty-three years. After effort, a hernia appeared, followed by vomiting, but as fæces and flatus continued to be passed, it was thought to be a case of strangulated omentum, or Richter's hernia. Operation disclosed the appendix in the sac. Hemsted likens this phenomenon to the straightening out of the inflating pipe of the inner tube of a bicycle tire. The patient had suffered from much flatulent dyspepsia. Turner observed a case of strangulated hernia in which the hernia had been reduced *en bloc* into the subperitoneal tissue. The peritoneal neck of the sac offered the constriction. Porter believes that enormous chances are taken in attempting taxis. Operation is often simpler and safer. He reports the case of a man aged forty-two years who had worn a truss for five years for a double inguinal hernia. The hernia escaped from under the truss and was reduced *en bloc* by a physician. The inguinal canal was empty, but later symptoms showed an intestinal obstruction and operation revealed the distended ileum in a peritoneal opening opposite the internal ring, while the empty sac was in the subperitoneal tissue entirely within the muscles, and bore no relation to the inguinal canal or the internal ring. There presented itself, therefore, a properitoneal or interstitial hernia. The inverted sac projected into the general cavity like the finger of a glove. Various conditions conduce to the formation of this variety of hernia, after apparently successful reduction of strangulated hernia, such as reduction into another preëxisting sac, incomplete reduction in obese subjects, etc.

In the operation for strangulated hernia, Whiteford emphasizes the fact that an essential factor in contributing to the successful result is the direct evacuation of the intestinal contents above the obstruction. This is possible only by draining the distended bowel through a large tube for several days. MacLaurin describes a case of strangulated hernia in a child fourteen days old in which circumcision had little or no curative effect on the rupture. Circumcision was performed when the child was seven days old, but this did not prevent a grave relapse of the hernia. Knaggs reports a case of strangulated femoral hernia in which gangrene was precipitated by an intraabdominal volvulus. Anderson reports a case of strangulated obturator hernia. Epiploitis is sometimes mistaken for strangulated hernia. Langton calls attention to the greater risk attending operation on strangulated

congenital hernia than in cases of ordinary strangulated acquired hernia.

Strangulated Inguinal Hernia Taken at First for Intestinal Obstruction by a Band; Peritonitis; Death.—This case is reported by Juillard. The patient was a man aged forty-five years with a right inguinal hernia. Symptoms of obstruction developed, but the hernia was found to be reduced as the finger could reach the internal ring through the inguinal canal without any hindrance. Pain was felt at the umbilicus. The diagnosis was made of internal strangulation, due to a band. When the abdomen was opened, general peritonitis was discovered. A loop of bowel was so closely fitted into the internal ring that it was impossible to withdraw it. The operation for strangulated inguinal hernia was done. The finger easily passed up to the internal ring and reached into the abdominal cavity, and was tightly grasped by the neck of the sac. The patient was in such bad condition that a thorough examination could not be made, but an artificial anus was formed in case a band was present. The patient succumbed to shock, however, in two hours. At autopsy the mark of constriction was seen on the bowel, although the calibre of the intestine was not lessened. No other band or cause of obstruction was discovered.

Stenosis of Intestine Following Strangulated Hernia.—Thomson, Kellock, and Battle call attention to the stenosis of the small intestine which sometimes follows strangulated hernia. In strangulated hernia the bowel is mechanically constricted, and although the grooves which are caused by the constriction generally disappear when the bowel is liberated, they may persist, and thus cause the symptoms of obstruction to continue or the injured intestine may so far recover as to allow of the passage of intestinal contents, but may later become the seat of fibrous stricture. In the latter case the symptoms of obstruction will reappear after a period of apparently normal condition. Thomson reports a case of this kind following strangulated, congenital, inguinal, left-sided hernia, while Caird has reported a case in which this lesion occurred in a case of femoral hernia.

Gangrenous Hernia.—The prophecies of Kocher and Mikulicz, in favor of the advantages of primary resection and suture over artificial anus, are being fulfilled. Hofmeister shows improved results. In twenty-five cases of primary resection he has had a mortality of forty per cent. He always begins his operation with Schleich's infiltration-anæsthesia, which is considered most advantageous in these cases, though on account of the pain from division of the constricting band and dissection of the sac, ether was resorted to in a few cases. The part of the bowel where the resection is performed should be perfectly healthy, especially at the proximal end. Beginning peritonitis does not contraindicate resection. In a series of 26 cases of gangrene of

the incarcerated intestinal loop, 17 were primarily resected with a mortality of 23.5 per cent. In 5, artificial anus was made, with a mortality of 80 per cent., while in the 4 in which the suspected loop was transposed, there was a mortality of 75 per cent.

Montgomery reports two cases in which enterectomy was successfully performed for gangrenous hernia. With respect to the suturing, he says that if the mucous membrane is first united, the peritoneal coats at the mesenteric angle can be accurately joined with little difficulty. According to Barker, there are three classes of gangrenous hernia. In the most hopeless class incision alone of the intestine is possible. In the other cases resection may be followed by either primary or secondary suture. If the proximal end be much distended, or the condition of the walls uncertain, suture offers the safer plan. This operation is shorter by eight to ten minutes than that of the primary suture. The mortality of the second part of the operation must be taken into account, as, according to Makins, it amounts to fifty-two per cent. If the condition of the patient warrant, and if the intestine be not much distended, the primary suture should be used.

Wallace reports the cases in St. Thomas' from 1888 to 1897, in which resection and primary suture were performed eleven times for gangrenous hernia with two successes. Death was generally due to exhaustion or gangrene and perforation of the gut higher up, for in only two of the nine fatal cases did post-mortem reveal defective sutures. Undoubtedly a more careful selection of cases with respect to the condition of the proximal end of the intestine—its distention and the extent of damage already accomplished—will lead to lessened mortality. Nine cases of gangrenous hernia in the last two years have been operated upon in the Manchester Royal Infirmary. The loop was merely incised in four of these cases. All were fatal in forty-eight hours. There was one successful case in which Juillard's method was used, the secondary suture being performed eight days after the resection. Four of the cases were resected and primary suture carried out; three of these were successful. In these are included the two cases reported above. The fatal case was one of resection of gangrenous cæcum. The button was not used in any acute case.

Wood and Stirling report successful cases of primary resection in cases of gangrenous hernia. According to Hofmeister, death in these cases is generally due to faulty technique or to the removal of insufficient bowel.

Fiessinger calls special attention to the success that he has had in the reduction of strangulated hernia by means of ether compresses. He advises letting the ether fall on the compress drop by drop in order to keep it constantly damp. He describes a case in which the

hernia had been strangulated for forty-four hours, which was reduced by this method in three-quarters of an hour. He warns the practitioner, however, against persisting with this method after a trial of thirty-six hours, for fear of gangrene. He explains the action of this treatment as a probable reflex which has a marked action on the vaso-constrictors.

Duke points out the importance, indeed the necessity, of an abdominal bandage in cases of pregnancy during the last four months. He believes that this precaution will prevent to a very great extent umbilical herniæ, as well as the lax and wrinkled abdominal parietes so often observed in women who have borne children. The lack of attention to this detail is sometimes the source of habitual constipation and many reflex symptoms. The trouble exists far more often than is suspected. The patient often complains to the physician of pain in the abdomen, but it requires a special examination that is frequently not considered necessary to detect a beginning umbilical hernia. The best method of determining this trouble is to have the patient lie on her back with the abdomen exposed, and then have her raise herself to the sitting posture. This will cause the protrusion of even a very small hernia.

Local Anæsthesia.—Cushing has paid particular attention to this method. He advocates its use in cases in which general anæsthesia is contraindicated. He believes it especially adapted for cases of strangulated and gangrenous hernia, which are both especially liable to pulmonary complications. This tendency is increased by general narcosis. In the shock and toxæmia coincident, local anæsthesia gives the best chance of recovery. From his experience this writer thinks that the operation is practically painless. The results of others, however, point to the necessity of being very familiar with the nerve supply of the region concerned, since much pain has been suffered in various cases on record. It is advised that a hypodermic injection of gr. $\frac{1}{8}$ to gr. $\frac{1}{16}$ of morphine be given three-quarters of an hour before the operation, and repeated shortly before the operation. Caution must be observed in this proceeding. The anæsthetic recommended by Cushing is Schleich's solution No. 2: Cocainæ mur., 0.1; morphinæ mur., 0.02; sodii chlor., 0.2; aquæ destillat., ad 100.00. This solution has not the disadvantages attributed to the usual cocaine solutions—that of breaking up and becoming toxic.

Meyer, as well as Cushing, has summed up the advantages and disadvantages of this method as follows: 1. Absence of dangers of general anæsthesia, both immediate and remote. 2. Absence (usually) of unpleasant sequelæ of anæsthesia. 3. The aid the patient can give the operator, that is, by coughing, so that the sac can be easily isolated. 4. The dressing can be applied to suit the patient at first. 5. Urinary

disturbances are less, catheterization being rarely necessary. 6. There is no backache. 7. The diet is the same as before operation. The disadvantages are: 1. According to Meyer, the severe suffering, mental and physical, which is caused, resulting in more or less shock. Cushing states that the pain will depend upon the familiarity of the surgeon with the anatomical distribution of the sensory nerves of the region. 2. The tendency on the part of the operator to hurry and slight certain steps. 3. The condition of neurasthenia, in which the operation may leave the patient; for often this condition resembles that following a railroad accident.

Stinson sums up the indications for local anæsthesia as follows: A. Local anæsthesia should be used in hernia operations when a general anæsthetic cannot be given without danger. 1. In some cases of strangulation in which there is great distention of the abdomen. In cases with a weak and rapid pulse. In cases of excessive vomiting, which persists after washing out the stomach. When the patient is constitutionally weak. In those cases in which the patient's appreciation of pain is blunt.

2. In marked organic disease of the heart, liver, lungs, and kidneys; in atheroma, and advanced acute and chronic affections of the respiratory tract.

3. In old age, in chronic alcoholics over fifty years of age, and in cases of great debility.

4. In marked arteriosclerosis.

5. In late operations in which the patient is liable to have some postoperative anæsthetic shock.

B. Local anæsthesia should be used in cases in which the patient will not submit to general anæsthesia.

General Anæsthesia.—Stinson gives the following suggestions: All mixtures, as A.C.E., ether, benzine, chloroform, etc., should be avoided. Ether and chloroform are preferable. Generally ether is preferable, as it is safer. Before giving chloroform, gr. $\frac{1}{40}$ of strychnine should be injected hypodermically. Morphine should never be given before chloroform. Care should be taken of the diet for twenty-four hours before, and the bowels should be kept open.

DISEASES OF THE AORTA.

BY

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IN the article on Diseases of the Blood-vessels, in Vol. IV., I gave a brief account of the macroscopical and microscopical changes which occur in the aorta as the result of disease. I now propose to give a more detailed account of these changes and to draw attention to certain points in the morbid anatomy of the aorta which are of the utmost importance in order to obtain a correct impression as to the pathological histology of the most common affections of arteries—namely, *atheroma.*

Structure of the Aorta.—I would first say a few words in the way of a reminder as to the normal structure of the aorta. In common with the other arteries of the body, the aorta possesses a sheath of connective tissue, but independently of this sheath it is formed of three coats named, from their relative position, internal, middle, and external. The inner coat consists of three different structures: (1) A layer of flattened epithelial cells. (2) A layer of delicate connective tissue containing a large number of anastomosing cells and cell spaces lying on a finely fibrillated ground substance. Longitudinal networks of very fine elastic fibres are also found, which are in continuity with the layer of elastic fibres of the next layer. (3) Elastic tissue in the form of longitudinal elastic network—the fenestrated membrane.

The middle coat consists of plain muscular tissue in fine bundles, disposed circularly round the vessel and made up of many layers. The elastic fibres attain a considerable development and alternate with the muscular fibres passing between the muscular bundles, as above stated. These elastic fibres extend into the subepithelial layer of the inner coat, so that the distinction between the inner and middle coats, as shown in section, is far less marked than it is in ordinary arteries. The external coat is composed of fine and evenly fitted bundles of white connective tissue, together with longitudinally disposed elastic tissue between the bundles.

The nutrient vessels which play an important part in the pathological conditions are distributed in the outer coat terminating in the middle coat.

Atheroma.

In my former article I detailed the changes which are found in acute and subacute aortitis. I shall therefore proceed to make some further remarks on atheroma. In the first place, a fact must be pointed out which has not yet received the recognition which its importance deserves, viz., that atheroma is the degenerative result of *all* lesions of the aorta, whether acute or chronic. Acute aortitis may result from external injury, overstrain, extension of disease from adjacent structures, or from certain general infections or intoxications. As a result of the irritations so produced atheroma may be manifested; the morbid changes thus produced are often indistinguishable from those resulting from chronic disease. The first effect is to be found in these layers of the aorta supplied by the arteria arteriorum. In case of overstrain the vessels are subject to intense internal pressure and give way at their terminals; therefore the earliest pathological changes are seen near where the vessels terminate—that is to say, in the middle coat and the adjoining fibres of the internal coat. This point I referred to in my previous article (Vol. IV., p. 467). The strain, then, does not occur mainly in the inner coat; otherwise this would be ruptured. On the other hand, as just mentioned, the deeper fibres of this coat are involved; subsequently to the rupture of the nutrient arteries, exudation corpuscles as well as fluid exudation pass into the more superficial layers of the internal coat, but do not reach the internal surface, which retains its smooth and polished appearance. This surface, however, is bulged as the result of the accumulation of the fluid, and this bulging is plainly seen in microscopic sections. It will be further observed that the fibres of this coat are opened out and divided from one another, being separated by œdema. This open network is amply sufficient to account for the bulging. These several points—bulging of the intima, separation of the fibres, and accumulation of exudation corpuscles—are well seen in microscopic sections and microphotographs.

It will perhaps serve the most practically useful purpose if I state my views from the standpoints of clinical observation and pathological investigation, including that of morbid anatomy, combined.

Acute and Subacute Aortitis.

Excluding direct injury and implication of the aorta in acute disease of the surrounding structures, we have to consider the operation of toxic agencies of some forms of acute disease at some periods of

their manifestation. I have already mentioned variola, scarlet fever, measles, and enteric fever as possible causes. I have also given evidence in support of the proposition that *malaria* may be a cause. It must be acknowledged that this is so but rarely, and the disease finds its expression as a cause only in the *late* periods of evolution. Moreover, it may very probably be that aortitis is seen only in *certain forms* of malaria.

I cited evidence in support of the proposition that influenza could be a cause, and further evidence which has come to me has confirmed this opinion. I have observed a few cases, some in the earlier periods when the diagnosis of influenza has been very decided, and others in which the symptoms have occurred later and the causal relation may be more doubtful, in which there have been symptoms of great distress referred to the sternum or to the epigastrium. The action of the heart has been much embarrassed, and symptoms of angina pectoris in some degree have been manifested. In some cases the pain has been very agonizing; in others the distress has not been acute, but has been chiefly expressed in terms of difficulty of breathing. In all, however, the attacks have been paroxysmal.

The mere occurrence of painful or distressful manifestations in paroxysms, even though accompanied by disturbances of the rhythm of the heart, would be insufficient to establish the diagnosis of the formidable disease under question, were it not that other signs come to one's aid. Physical investigation demonstrates either a local bulging of a part of the aorta or else there become manifest, perhaps subtly and unexpectedly, the physical evidences of a local and apparently slight impairment of the aortic valves. A slightly pronounced systolic murmur or a diastolic murmur or both murmurs combined may be observed, perhaps not constantly but at intervals. I have noted in one case a localized bulging (as of aneurysm) of the abdominal aorta below the epigastrium.

Close investigation has convinced me that the following is the mode of morbid evolution: The active microorganisms of the disease penetrate the regions of the aorta affected. They are arrested in the fine capillaries, but their toxins constitute an irritant whose field of operation is wider; the meshes of the middle and internal coats are opened out by the resulting œdema. If the coronaries are affected, the mechanical block arising from the prominence of the endothelium and adjoining inner coat causes a direct impairment of the circulation within the heart structures.

But the process of destruction (necrosis) goes on and the endothelial layer may be lifted up as a herpetic bleb or may become ulcerated. With and during this process the degenerative processes of atheroma occur if there is time enough. So there are either the gelatiniform

patches or the firmer and harder fibrous or calcified patches according to the time of evolution. Restitution is possible in this way; the degenerated patch may be in an unimportant position, and the firmness and hardness of fibrosis and calcification may prevent any aneurysmal bulging.

Treatment.—Giving these data from the fields of clinical observation and morbid anatomy their due weight, it follows that in treatment the two first principles should be rest and freedom from suffering.

Rest in a comfortable posture is the first consideration. Local applications to the sternum and neighborhood are generally futile, but I think the application of ice bags does good in some cases. I have tried the continuous galvanic current. I am not sure that it has had a very beneficial effect, but it gives promise.

Internally I have found nothing better in most cases than phenacetin in five-grain doses with one grain of camphor. These may be given in wafer cachets once, twice, or thrice in the twenty-four hours. In some cases phenacetin is not so effectual as antipyrin, which should be given in fifteen-grain doses with twenty minims of compound tincture of camphor and an ounce of chloroform water. Phenacetin is, however, on the whole the best, and opiates are to be avoided if possible. Trinitrin, the nitrites, and inhalations of nitrite of amyl are to be used in addition if necessary, but with some caution, for it is only a *temporary* relaxation of the arterioles that we desire to attain.

With all this treatment chiefly directed to the hope of protraction of the case and relief of suffering, some direct antiseptic, as sulphocarbolate of sodium in thirty-grain doses dissolved in cinnamon water may be administered every four hours. It must be acknowledged, however, that the difficulties in the very acute cases, just as in ulcerative endocarditis, are very great, but there is hope in protraction and the occurrence of fibrosis.

Chronic Aortitis.

In the chronic cases there is more chance. Then we have to trace other causes of morbid initiation; as I have before said (Vol. IV., p. 49), these causes as clinically observed may be: (1) Senility; (2) muscular overstrain; (3) gout; (4) over-indulgences; (5) syphilis; (6) malaria. I will endeavor to trace the minute evidence of the operation of these causes, taking *overstrain* to start with. Where is the vascular overstrain to the point of rupture first met with? Not within the aorta, as so many have thought, because in such case the morbid changes would commence in a sclerosed or ruptured endothelium. They do not. They do commence in distention and rupture of the arterioles, or capillaries proceeding therefrom, of the nutrient arteries of the aorta. In these, in the special region affected, the

sudden overstrain usually from muscular effort becomes manifested, rupture ensues, and changes occur such as I have just described. In the case of gout there must be something solid or particulate primarily to block the arterioles, and what so probable as the insoluble urates? Analogous causes, urates or some other producers of perverted metabolism, are probably the causes in the various forms of over-indulgences. In syphilis it is most probable that an arteritis occurs in the fine arteries of the coats of the aorta, just as in the fine cerebral arterioles as crucially demonstrated. The first cause is more likely to be a toxin than a microorganism.

Treatment.—Premising that no hard-and-fast lines during the observation of cases can be drawn between the acute and chronic, the element of time being the only practical mode of determining, I have little to add to the therapeutic notes I have already given (pp. 477 *et seq.*). I would, however, strongly emphasize in chronic cases the advantage of air cure and the absence of worry. The combination of these therapeutic agencies is shown in the advantage of sea voyages and sojourns in various air-cure places where no bath treatment comes in as part of the therapeutics. There can be no doubt, however, that in many cases the addition of bath treatment is a useful one. A prolonged course of iodides, especially the iodide of sodium in small (gr. iij.–v.) doses, especially with arsenic (Fowler's solution, ♏ iij. thrice daily), is very valuable. The treatment, as by phenacetin, for freedom from pain and discomfort must, however, be long persisted in.

THE BLOOD.

BY

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General Chemistry.

SPECIFIC GRAVITY.—In health the specific gravity of the blood may vary from 1.040 to 1.062. It is safe to assume that venous or arterial blood has undergone some pathological alteration if its specific gravity falls outside of these limits. Age and sex exercise, under normal conditions, a certain influence upon the specific gravity of blood; thus in men the average is 1.059, in women 1.056, in boys 1.052, and in girls 1.050. Generally speaking, the specific gravity of venous blood is higher than that of arterial. The blood in disease may show specific gravities from 1.025 to 1.068. In nephritis, chlorosis, anæmias in general, as also in pulmonary phthisis and cachectic conditions, the specific gravity of the blood is subnormal; while in fevers, valvular cardiac diseases, and obstructing jaundice it is hypernormal. As the result of recent investigations it is certain that, with the exception of nephritis, circulatory disturbances, leukæmia, and possibly post-hemorrhagic and inanition anæmia, the specific gravity of the blood varies directly with the amount of hæmoglobin present. In many cases, therefore, reliable hæmoglobin estimations may be based upon the results of specific gravity determinations. Thus the clinician who may not be equipped with a satisfactory hæmometer is provided with a ready method by means of which he can obtain a trustworthy opinion in regard to the amount of hæmoglobin present in a given case.

Methods for Determining the Specific Gravity of Blood.—No method for this purpose has as yet been devised which approaches in accuracy that of Schmaltz and Peiper, but since the technique here involved requires the use of a delicate balance, the employment of this method does not come within the scope of most clinicians. Hammerschlag's method, a description of which is contained in Vol. VII. of this work, gives fairly accurate results and is very easy of application. Roy's method is as accurate as Hammerschlag's, and has the further

advantage that for its employment only glycerin, water, a urinometer, and a few test tubes are required. In place of the latter, in case of necessity, ordinary glass tumblers will suffice. A series of mixtures are made, with the glycerin and water, whose specific gravities vary between 1.025 and 1.068, the intervals being five points each. A drop of blood is placed in each mixture. That in which it remains suspended in the fluid corresponds to the specific gravity of the blood. If it is found that the drop does not remain so suspended in any of these mixtures, a new series should be made in which the specific gravity varies at one-point intervals between the limits of those mixtures in which the desired result was most nearly obtained in the first series, and the experiment repeated as before. In this manner an accurate estimation of the specific gravity of the examined blood may be obtained. The chief disadvantage of Roy's method is that it may be necessary in any given case to use quite a number of blood drops and thus considerably annoy the patient. For this reason, when chloroform and benzol are available Hammerschlag's method is to be preferred, as in recent years its employment has been conducted by the use of one mixture and one drop of blood. Two especial precautions should be taken in the carrying out of any specific gravity test: (1) No pressure should be used in obtaining the blood drop, but this must appear as the result of simple puncture. (2) In making a series of observations on the same patient these should be conducted at the same hour of the day, since it has been shown that the specific gravity of the blood under both normal and pathological conditions undergoes diurnal variations.

REACTION.—The reaction of the blood is alkaline. The degree of alkalinity is best expressed in terms of sodium hydrate. So expressed under normal conditions, it corresponds to 182 to 218 mgm. of this substance for every 100 c.c. of blood. Different authors, however, vary in regard to the validity of these figures; thus v. Jaksch gives 260 to 300 mgm., and Canard 203 to 276 mgm. as the normal. Generally speaking, men show higher figures than women and children. The process of digestion and exercise normally exert a certain influence upon the alkalinity of the blood. At the beginning of digestion, when hydrochloric acid is being secreted in large amounts, the alkalinity of the blood increases, while later on it diminishes. A notable decrease is brought about by violent muscular exercise, due no doubt to an excessive production of acids in the muscles. Cold bathing is followed by an increase in the alkalinity of the blood, and coexistent with this there is also an increase in its bactericidal power. Under pathological conditions the alkalinity of the blood is frequently markedly diminished. Such is especially the case in anæmia, leukæmia, nephritis when accompanied by uræmia, various hepatic diseases, dia-

betes, carcinoma, various cachectic conditions, pseudoleukæmia, poisoning with carbon monoxide and acids, also in high fevers. It has been supposed that in gout a diminished alkalinity exists between the attacks and becomes hypernormal during the attack. The correctness of this view has not as yet been definitely proven.

Methods for the Determination of the Reaction of the Blood.—In recent years the only methods for this purpose which have received serious consideration at the hands of competent investigators are the alkalimetric—those which determine the degree of alkalinity by titration. Of such only those of v. Jaksch and Löwy deserve mention. Jaksch's method is a modification of that originally devised by Landois; it is open, however, to numerous objections and is much too complicated for clinical use. Löwy's method is the most recent and in our present knowledge seems to be the most exact. Five cubic centimetres of the blood is allowed to flow into a small flask provided with a long and partially graduated neck, and which contains 45 c.c. of a 0.25-per-cent. solution of ammonium oxalate. This prevents coagulation and dissolves the hæmoglobin from the stroma of the red blood cells. This mixture is then titrated with a one-twenty-fifth normal aqueous solution (3 gm. to the litre) of tartaric acid, using lacmoid paper, soaked in a concentrated solution of magnesium sulphate, as an indicator. The lacmoid paper is prepared as follows: 100 gm. of resorcin, 5 gm. of sodium nitrate, and 5 c.c. of distilled water are heated on an oil bath to just short of 110° C. After momentary cooling it is likewise heated to 115° or 120° C., until all the ammonia is driven off and a residue of pure blue color alone remains. This is dissolved in water and precipitated with hydrochloric acid. This precipitate is removed by filtering and washed in water. It is then dissolved in absolute alcohol and allowed to evaporate in an atmosphere free from ammonia. One gram of the reddish-brown residue is dissolved in 1,000 c.c. of forty-five-per-cent. alcohol. Strips of Swedish filter paper are immersed therein and allowed to dry. In the titration 1 c.c. of the one-twenty-fifth normal tartaric acid solution corresponds to 0.0016 gm. of sodium hydrate. It is therefore evident that 0.0016 multiplied by the number of cubic centimetres of the tartaric solution necessary to neutralize the solution containing the 5 c.c. of blood will represent the alkalinity of 5 c.c. of the blood expressed in grams of sodium hydrate. This multiplied by 20 gives the amount of sodium hydrate in grams in 100 c.c. of blood. This multiplied by 1,000 gives the amount of sodium hydrate expressed in milligrams in 100 c.c. of blood. This is the final determination required. Engel has recently devised an apparatus (the akalimeter), by the use of which the technique involved in Löwy's method is materially simplified.

General Composition.—The following table gives a schematic repre-

sentation of the general chemical composition of the blood. The figures are those given by C. Schmidt as representing the proportions present in 1,000 parts.

	Man.	Woman.
Corpuscles	513.1	369.2
Water	349.7	272.6
Hæmoglobin and globulins	159.6	120.1
Mineral salts	3.7	3.55
Plasma	486.9	603.8
Water	439.	552.
Fibrin	3.9	1.91
Albumins and extractives	39.9	44.79
Mineral salts	4.14	5.07

In addition to the above the following substances are present in varying quantity in normal blood: fat, soaps, carbohydrates, cholesterin, and lecithin.

Proteids and Albumins.—Taking normal blood in its entirety, the following proteids and albumins are found therein: hæmoglobin and globulins, fibrinogen, serum globulin, and serum albumin. Upon coagulation the fibrinogen is split up by a special ferment. Fibrin is thus formed, and in the serum a new albuminous body, fibrino-globulin, is found. This special ferment—the fibrin ferment—is thought by some to be produced by the leucocytes. Its action is increased by calcium salts.

Under *pathological* conditions the proteids as a class may be relatively increased in amount in the blood. It has not as yet, however, been demonstrated that an absolute increase ever occurs. All diseases in which the normal amount of water is reduced in the blood are accompanied by a relative increase in its proteid constituents. Both a relative and an absolute decrease in the amount of proteids in the blood is, however, frequently observed. This may be brought about by either of two factors: (1) Direct loss of proteids due to hemorrhage or malnutrition; (2) an increase in the amount of water normally present in the blood.

Tests for Estimating Total Amount of Albumin in the Blood.—No tests for this purpose have been devised which come within the scope of the clinician. For laboratory use either of two methods may be employed: (1) Precipitation of the albumins by an excess of alcohol and weighing the dried precipitate; (2) estimating the total nitrogen present in the blood and multiplying the result by 6.25. The second method is by far the more accurate and is the one in most general use.

The amount of *fibrin* present in the blood may be increased or decreased under various pathological conditions. An increase is called *hyperinosis*, and has been observed during the course of pneu-

monia, pleurisy, acute articular rheumatism, and occasionally erysipelas. A decrease is called *hypinosis*, and is found in malaria, nephritis, pyæmia, and pernicious anæmia.

For *determinations* of the *amount of fibrin* present, 25 to 50 c.c. of the blood is necessary. This is defibrinated in the ordinary manner and the whole carefully weighed. The fibrin is then allowed to settle, washed in normal salt solution, filtered, and boiled in alcohol to extract the fat, cholesterin, and lecithin. It is then dried at 110°–120° C. and carefully weighed upon cooling. The results may be controlled by comparing the weight of the total blood subsequent to defibrination with the weight of the fluid remaining after defibrination plus the weight of the dried alcohol extractives plus the weight of the fibrin.

The presence of *peptone* in large quantities in the blood has been announced by v. Jaksch in the blood of leukæmia. Matthes has not been able to confirm this, and regards the peptone described by Jaksch as a deuteroalbumose.

For *determining the presence of peptone* in the blood the same methods may be employed as for its detection in the urine. Bang's method is preferable, but Salkowsky's may be used.

Albumoses have been found in the blood by various authors under diversified pathological conditions generally associated with albumosuria. In *testing for the presence of albumoses* all other proteids should be at first removed from the blood. The biuret test is then applied to the filtrate. If the reaction is positive albumoses are present.

Mineral Salts.—The mineral salts of the blood are those of potassium, sodium, calcium, magnesium, iron, chlorine, and phosphorus. The corpuscles contain a larger proportion of potassium salts and phosphorus than does the serum, while the latter is richer in sodium salts and chlorine than the former. The amount of sodium chloride in the plasma is more than enough to prevent the solution of the hæmoglobin by the water of the blood, and the plasma is thus said to be "hyperisotonic." Under normal conditions this amount of sodium chloride remains practically constant, irrespective of the amount of the salt ingested. According to Baumgarten, the phenomena of hæmolysis and bacteriolysis are due to the fact that plasma of one animal is "hypoisotonic" for the erythrocytes of another animal, or for certain microorganisms in the case of bacteriolysis. Such a "hypoisotonic" condition of the plasma may be normal to the animal or it may be artificially produced. A full consideration of Baumgarten's theory will be found under the section on vital properties of the serum.

Carbohydrates.—*Glucose* in small quantities is a normal constituent of the blood. Under pathological conditions the greatest increase in the blood glucose occurs in diabetes. It has been claimed by some that

a differential diagnosis between carcinoma and sarcoma can be made by a determination of the amount of sugar present in the blood—sarcoma showing no increase over the normal, while carcinoma gives a constant and fair increase in this carbohydrate. Freund originally advanced this view, and Trinkler confirmed his opinions. While it is true that a certain number of cases of sarcoma show no increase of glucose in the blood, it is not true that such is always the case, and in our present knowledge concerning the various pathological conditions which are accompanied by an increase of glucose in the blood it cannot be said that a reliable differential diagnosis between carcinoma and sarcoma is to be made in the manner above indicated. At the best the determination of the amount of blood glucose in these diseases is to be considered only as confirmatory to other more reliable appearances.

Blood Tests for Glucose.—In order to test the blood for the presence of glucose either qualitatively or quantitatively it is necessary as preliminary to remove all proteids therefrom. This may be accomplished in various ways:

First Method.—Fifteen to thirty grams of the blood is mixed with an equal weight of finely powdered sodium sulphate and a few drops of acetic acid added. This is brought to the boiling point and maintained there until the coagulum becomes dark in color. Water is then added to bring the quantity up to its original volume, and the whole filtered through muslin, after which the filtrate is passed through filter paper.

Second Method.—The same amount of blood as used in the first method is mixed with four or five times its volume of alcohol (ninety-six per cent.) and a few drops of acetic acid added. This is then left alone for from five to six hours. It is then filtered and slowly heated until the alcohol is driven off. If any albumin separates, more alcohol is added, and the process repeated. The final residue is dissolved in water and the sugar contained therein estimated.

Third Method.—To the same amount of blood as used in methods one and two 200 c.c. of distilled water is added, together with six drops of a solution consisting of ten parts acetic and one part lactic acid. This is boiled for eight to ten minutes and filtered. The coagulum is washed with hot water and thoroughly pressed out in muslin. The filtrates thus obtained are mixed and evaporated to a small volume. If any coagulum forms it is filtered off.

The end products obtained by the use of any one of these three methods is then tested for sugar by any of the methods in ordinary use. Knapp's method is recommended if the second process above described is employed.

Williamson's Diabetic Blood Test.—R. T. Williamson has devised a

method by the use of which an increase in the normal amount of blood glucose may be detected. It is not quantitative, but is of utility in that it is of simple execution and can be used with ease by the clinical practitioner in the routine examination of diabetic cases. He can thus determine independent of urine examinations whether or not glucose is present in excess in the blood. The technique is as follows: Twenty cubic millimetres of blood are obtained from a finger prick in the capillary pipette which accompanies Gowers' hæmometer. This is blown out into a test tube and mixed with double its quantity of distilled water. To this is further added 1 c.c. of aqueous methylene blue (1:6,000) and 40 c.mm. of a six-per-cent. aqueous solution of potassium hydrate. A control is made with non-diabetic blood. The two specimens are then placed in boiling water for from two to three minutes without shaking. If sugar be present in excess of the normal in the tested blood, the mixture containing it will lose its blue color and become a yellowish-green or yellow. Otherwise no change will be produced. From a personal clinical experience I can unqualifiedly recommend this test as of ready execution and of value in the observation and treatment of diabetes.

Bremer's Test for Diabetic Blood.—Bremer has shown that diabetic blood, when properly smeared and fixed upon a glass slide, if exposed for from one and one-half to two minutes to a one-per-cent. aqueous solution of Congo-red, methylene blue, or eosin, fails to take the characteristic red color, and either does not stain at all or becomes simply a light orange color. On the other hand, such diabetic blood, if immersed in a similar solution of Biebrich's scarlet, takes the color well, while non-diabetic blood refuses to stain. For this purpose the blood should be smeared in a wave-like manner, and fixed at a temperature of from 130° to 135° C. for about two minutes. It has been conclusively shown that the presence of this reaction is not due to the presence of glucose in the blood, and that in all probability it is dependent upon a polychromatophilic degeneration of the erythrocytes. So far as we at present know, this reaction is pathognomonic of diabetes, and may be obtained either previous or subsequent to the appearance of glucose in the urine. Its diagnostic importance in this disease, therefore, seems certain.

Glycogen.—While there is some diversity of opinion upon the subject, there appears to be no doubt that glycogen is present in small quantities in the blood of healthy individuals. In such, however, it is to be found only in the plasma. Its presence in the leucocytes is believed to be always a pathological phenomenon. The most recent work upon this subject has been done by Locke and Cabot, and is fully considered in the section on Iodophilia.

Test for Blood Glycogen.—A rough method for demonstrating the

presence of glycogen in blood is as follows: Place a drop of blood between two cover glasses, and when dried place them, smeared surfaces up, in a small covered jar containing a few iodine crystals. When the films have become a dark-brown color, mount them in a saturated solution of levulose and examine microscopically with Leitz No. 7 or oil-immersion lens. All glycogen granules will be stained a deep mahogany. The erythrocytes are the color of iodine, while the leucocytes are practically colorless.

Uric Acid and Xanthin Bases.—These substances are found only in traces in normal blood. Pathologically they are present, however, in a large number of conditions. Among such may be mentioned gout, rheumatism, pneumonia, acute and chronic nephritis, gastritis, pernicious anæmia, leukæmia, tuberculosis, typhoid fever, and pleurisy.

Tests for Uric Acid and Xanthin Bases in the Blood.—The technique which is involved in the quantitative determination of these substances in the blood is far too intricate for clinicians to handle. The Ludwig-Salkowski and Hopkins methods give the best results. Large amounts of these substances may, however, be detected by Garrod's test, which comes within the scope of the practitioner. The technique is as follows: Five to ten cubic centimetres of the blood serum is treated with six to ten drops of a thirty-per-cent. solution of acetic acid. A linen thread is placed in this fluid and the whole put in an ice-box for eighteen to twenty-four hours or longer. The thread is then withdrawn from the liquid, and if these substances were present in large amount therein crystals will be seen adhering to the thread. These may then be examined microscopically and their nature demonstrated.

Fat and Fatty Acids.—The fat normally present in the blood may be increased in amount in a multitude of conditions. The greatest increase occurs in severe diabetes. Among other diseases which show an increase are nephritis, tuberculosis, malaria, liver diseases, phosphorus poisoning, etc.

Tests for Fat and Fatty Acids in the Blood.—1. *Fat.*—Prepare ordinary smears and mount in five-per-cent. osmic acid. Fat droplets are colored black.

2. *Fatty Acids.*—Add to 20–30 c.c. of blood an equal weight of sodium sulphate. Evaporate to dryness. Add absolute alcohol and again evaporate to dryness. The crystals of the fatty acids thus obtained should be examined microscopically and their nature demonstrated.

Urea.—Traces of urea are found in the blood under normal conditions. Whenever for any cause the elimination of urea is impeded, an increase in the amount of this substance normally present in the blood occurs. Such defective elimination is principally caused by diseases of the kidney and intestines, and possibly also by diseases of the

liver. In our present knowledge concerning urea, very little that is of practical importance is to be obtained from blood urea estimations. Research along this line is, however, greatly to be desired.

Tests for Urea in the Blood.—No method for this purpose has as yet been devised which comes within the scope of the clinician. For laboratory use Hoppe-Seyler's method gives the most accurate results.

Bile Pigments and Acids.—These substances are not found in normal blood. Under pathological conditions they are usually found in the blood only when their presence in the urine can also be demonstrated. Occasionally, however, they may be encountered in the blood when not present in the urine.

Test for Bile Pigments.—Ten to fifteen cubic centimetres of blood is allowed to coagulate in a glass bulb. The serum is drawn off with a capillary pipette, filtered, and solidified at 80° C. in a very thin layer. The serum thus coagulated should be free from hæmoglobin and red blood cells or the integrity of the test will be interfered with. If bile pigment is present in the serum tested under the above conditions, the dried solidified layer soon takes a light green color; otherwise it retains its straw color.

Tests for Bile Salts.—The proteids are removed in 20 to 30 c.c. of blood by precipitation with alcohol. This precipitate is removed by filtration and the bile salts which are present in the filtrate are precipitated therefrom by the addition of lead acetate and ammonia, and thus converted into their corresponding lead salts. This precipitate is washed with water, boiled with alcohol, and filtered. Sodium carbonate is added in excess to the filtrate and the mixture is again filtered and the filtrate evaporated to dryness. To the residue alcohol is added. This is subsequently distilled off when the biliary salts of sodium will crystallize out. These crystals are dissolved in water and two-thirds of the volume of concentrated sulphuric acid added. This solution is then tested according to Pettenkofer's method.

Acetone.—Acetone is not present in normal blood. Under pathological conditions it appears in a variety of conditions. During the past few years considerable attention has been paid to the presence of this substance in the blood of diabetic patients. It is believed that the occurrence of diabetic coma is directly dependent upon the increase in the amount of acetone and organic acids present in the blood in this disease. It appears that this amount can be correctly estimated by appropriate uranalysis, and hence blood examinations for its presence are not necessary.

Test for Acetone.—Dennige's is the simplest and is fairly accurate. The technique is as follows: 3 c.c. of the blood is mixed with 30 c.c. of Dennige's reagent and allowed to stand until the precipitate has settled. This is removed by filtration and to the filtrate more reagent

is added and the mixture again filtered. This process is repeated until no precipitation is produced in the filtrate by the addition of the reagent. The filtrate is then acidified with sulphuric acid and the mixture heated. If acetone or diacetic acid is present, it is thrown down in the form of a white precipitate, which is soluble in an excess of hydrochloric acid. By making a series of tests on diabetic blood the quantitative proportions of these substances present may be estimated with fair accuracy.

The Serum.

The chief advances in our knowledge of the blood serum which have been made during the past few years relate to its vital properties. That is, its power under normal or pathological conditions to produce hæmolysis, bacteriolysis, immunity to toxins, agglutination of erythrocytes, or microorganisms, and under certain conditions the precipitation of certain substances in bacterial filtrates or other fluids against which such serum is active. It is probable that more has been written in regard to this important and interesting subject during the past two or three years than in regard to any other topic in experimental or clinical medicine. Ehrlich, Bordet, and Baumgarten have especially concerned themselves with these phenomena, and to-day are the exponents of theories to one or another of which all competent observers announce their adherence. As a correct understanding of these phenomena is of vital importance for an intelligent theoretical and clinical consideration of the bacterial diseases at least, it seems essential to enter into a somewhat detailed description of them. Beginning with the fundamental principles of cell physiology and pathology as laid down by Virchow, Ehrlich states that it is certain that the normal protective substances of the serum and those artificially produced as the result of infection are entirely similar in their mode of origin. He first considers the mode of action of the so-called antitoxic substances present in specific antisera. If we take a given quantity of any specific antitoxic serum and add to it different *homologous* toxin bouillons, we find that it neutralizes in different cases various quantities of such toxin bouillons, and that the quantities previous to neutralization possessed a different toxic power. This shows that whatever laws govern the neutralization of toxin by antitoxin, they do not *apparently* follow those of ordinary chemical equivalence. If we take a given portion of such toxic bouillon, having previously ascertained its toxic power and the quantity of antitoxin necessary to neutralize it, and preserve it for a certain time, we find at the end of this time that it requires the same amount of antitoxin to neutralize it as it originally did, but that its toxic power has been markedly reduced. This shows that the toxin molecule contained two substances or groups of

substances, one of which was concerned in the neutralization process and was stable, while the other constituted the toxic property and was unstable, being very much reduced in amount the longer it was preserved. Ehrlich calls the first of these substances the "haptophore" group and the second the "toxophore" group. "Toxoids" are toxins which have retained their haptophores, but entirely lost their toxophores. The presence of such toxoids accounts for the apparent violation of the laws of chemical equivalence above noted. Two facts show that the haptophore group is the chief factor in the neutralization of toxins by antitoxic sera. First, toxoids upon inoculation are abundantly able to produce antitoxic sera; and second, toxins whose haptophore groups are entirely used up are no longer able to produce such sera. In order to grasp the subject in its entirety it is necessary to consider the functions of the living body in the formation of antitoxic sera. It is a firmly established law in therapeutics that chemical substances when introduced into the body act only upon certain cells. In other words, certain cells of the body show a predilection for certain substances. Furthermore, such substances do not enter into a firm chemical combination with such cells, but are found stored therein and may be extracted therefrom by various processes. In accordance with this it cannot be denied that certain substances enter into such combination with the albumin molecule. This is also to be applied to the nutritive processes of cells, which accordingly are to be considered as synthetic processes. In conformity with this idea in living protoplasm, there are numerous groups called "side-chains" or "receptors," which possess a maximum attraction, so to speak, for certain nutritive substances and by means of which these substances are retained and anchored to the cell. These receptors are multitudinous in number. Now the haptophore group of the toxic molecule being non-poisonous in character acts as a nutritive substance, finds its receptor in the protoplasm of the cell, and anchors the whole toxin molecule to the cell. In this manner the cell is brought under the deleterious influence of the toxin. If the influence upon the cell of the toxophore group of the toxin molecule is not too severe, a regeneration process in accordance with a universal law in nature is set up, and the haptophore receptor having been used up in the process is replaced. By a continuation of this process there finally comes a time when the haptophore receptors are so abundantly produced that they can no longer be retained in the cell and they pass into the blood. When this takes place they seize the toxin molecule in the blood and prevent its entrance into the cell where it can do harm. Accordingly the toxin-immunizing property of antitoxic sera is entirely dependent upon the quantity of haptophore receptors in such sera. Of course it is to be understood that the toxophore group of the toxin molecule also finds

its receptor in the cell protoplasm, but this is not concerned directly in the production of immunity to toxins, as it is soon disposed of by the poisonous action of the toxophore.

When we consider the questions of hæmolysis, bacteriolysis, precipitation, and agglutination, the conditions become very much more complicated than those just described in connection with the production of antitoxic sera. As these processes are identical in nature, the study of hæmolysis will serve to illustrate the others. Horses inoculated with the blood of rabbits produce a serum which destroys the erythrocytes of the latter animals. When such serum is heated for one-half an hour at 55° C. it loses this property, but regains it when certain *normal* sera are added. From this it is seen that in hæmolytic sera two substances produce the hæmolytic action. One of these is present only in immune sera and is stable, and the other is present in normal sera, being unstable and easily destroyed by heat. The first of these is called the "immune body" and the second the "complement." By experimenting with sera which contain only an immune body or complement, it is shown that the red blood cells are not able to take up the complement when it is alone present, but only when the immune body is also present. Nevertheless they take up the immune body when it is alone present; this, however, does not produce hæmolysis. It is thus seen that the immune body is the medium which anchors the complement to the red blood cell, which latter brings about its destruction. Ehrlich believes that this immune body possesses two kinds of haptophore groups, one of which becomes united with its receptor in the erythrocyte protoplasm, and the other binds the complement to the erythrocyte. In order to express this double action of the immune body, he calls it the "amboceptor." The complement possesses a constitution analogous to the toxin. It has a haptophore group, by means of which the amboceptor unites it to the erythrocyte and through which anticomplements are produced in a manner entirely similar to that by which antitoxins are formed; it also possesses another group, which is the analogue of the toxophore group of the toxins and which brings about the destruction of the red blood cell. The action of this group is called "zymotoxic." Ehrlich holds that the origin of the immune body and complement is cellular. The first is a receptor of high molecular composition. Its presence in immune sera is brought about in a manner entirely similar to that given for the production of the antitoxin receptor. The complement is to be regarded as a normal cell secretion.

Bordet's views respecting hæmolysis are similar to Ehrlich's, with the exception that the first-named author holds that no union takes place between the immune body and complement, but that the immune body in some manner prepares the red blood cells for the destructive

action of the latter. The decision of this point is of practical as well as theoretical interest, and at the present time is attracting the attention of a large number of observers, especially in Germany and France. Max Matthes has recently shown that the immune bodies at least have no deleterious action upon the erythrocytes, and upon this ground claims that the supposition that they prepare these cells for the action of the complements is not well founded. Such reasoning, however, is by no means sound. All that we can say at the present time is that we are without sufficient knowledge to decide the exact mode of action of the immune bodies and complements.

Whatever may be the *modus operandi* of the immune bodies and complements, Bordet and Ehrlich both agree that hæmolysis and bacteriolysis are essentially fermentative processes. P. Baumgarten, on the other hand, holds that these processes are physical in nature and are essentially diffusion processes due to the presence of osmotic currents. This is shown by the fact that hæmolysis takes place when erythrocytes are introduced into certain anisotonic salt solutions. That such hæmolysis, however, is less active than that which ocurs in serum proves that osmosis is not the only causative factor operative, but that there are present in serum certain substances which favor and accelerate the osmotic process. These substances correspond to the immune bodies of Ehrlich, and Baumgarten regards them as identical with the agglutinins. Baumgarten, in support of his hypothesis, cites the following postulates: (1) The digestive action of ferments upon red blood cells is slow. Trypsin solutions require five or six hours before an appreciable result is obtained. Hæmolysis in heterogeneous serum is, however, complete at the latest in two hours. (2) Serum is a fluid containing substances which produce osmosis. It is entirely conceivable that the sera of different animals contain different amounts of such substances, and, furthermore, that the osmotic pressure in the erythrocytes of different animals is different. (3) The fact that one-half hour heating of active serum destroys its hæmolytic but not its agglutinating power. It is well known that the heating of osmotic fluids destroys their activity. (4) Such active serum when heated may have its hæmolytic power restored by the mere addition of hyperisotonic salt solution. It is not at all necessary that normal serum be added in order that this result may be produced. (5) The direct microscopical observation of the process of hæmolysis favors the view that it is essentially physical rather than digestive in nature. While many of these arguments advanced by Baumgarten carry considerable weight, it is nevertheless true that at the present time the majority of observers refuse to accept his conclusions.

Erythrocytes.

Origin and Formation.—Two views exist to-day with respect to the origin of the erythrocytes:

1. Hiss, Remak, Kölliker, Wissosky, Klein, and Stricker have shown that the first appearance of hæmoglobin in cells occurs in some of the cells of the mesodermal cords which form the initial capillaries. When the vessel is formed these cells lie free in the lumen as nucleated red blood discs. These proliferate by mitosis and eventually give rise to the non-nucleated erythrocyte. The exact manner in which the nucleated erythrocyte passes into the non-nucleated form has given rise to much discussion, and cannot be said to be definitely settled at the present time. Some observers hold that the nucleus gradually fades. The final stages of such disappearance have not, however, been successfully demonstrated. Others claim that the nucleus is extruded from the cell either en masse or fragmentarily. Still others think that a combination of these processes is present, and the recent studies of Maximow would seem to substantiate this view. He holds that a portion of the nucleus is permanently retained within the cell in a finely granular form.

2. According to the second theory, the erythrocytes originate from certain large connective-tissue cells. The erythrocytes are first seen as globules of hæmoglobin which lie in the body of these cells. The connective-tissue cell eventually becomes a capillary and the erythrocyte is set free. It is never nucleated. Nucleated red blood cells are an entirely different species and originate as per the first theory. This so-called intracellular origin of the erythrocytes has been especially advocated by Schäfer, Ranvier, and Hayem, but has not found favor with the majority of histologists.

Much discussion has taken place in regard to the so-called common origin of red and white blood cells, and the question is as yet by no means decided. Müller is the especial advocate of such common origin, while Löwit, Bizzozero, and Denys maintain that they have a separate origin. Extensive research is necessary for the final decision of this question.

Site of Formation of Erythrocytes.—1. *In early embryonal life.* The formation of erythrocytes takes place in many tissues and follows the development of the capillaries.

2. *In late embryonal life.* Erythrocytes are principally formed in the liver, to a fair extent in the spleen, and as birth approaches in the bone marrow.

3. *After birth.* Erythrocytes are exclusively formed in the bone marrow.

Pathological Alterations in Erythrocytes.

1. *Poikilocytosis.*—This term is applied to the appearance of erythrocytes which have lost their normal form. They are usually shrunken and pear-shaped in contour, but a great diversity of shapes may be seen. Poikilocytosis is most frequently met with in severe anæmias, but is often observed in other conditions which show a degeneration of the various blood elements. It should be noted that a similar appearance may be artificially produced in the preparation and staining of blood smears, hence when an endeavor is being made to demonstrate its presence fresh fluid blood should always be examined.

2. *Polychromatophilic Degeneration.*—This term applies to that form of degeneration of the erythrocytes in which they do not take the eosin stain in the characteristic manner and show a certain affinity for basic dyes. Erythrocytes undergoing this form of degeneration when stained in smears with hæmatoxylin-eosin or eosin-methylene blue may show all gradations of color from a bright red to a distinct blue. Physiologically polychromasia is observed in certain erythrocytes of the embryo. Pathologically it is present in anæmia, either primary or secondary, and in the various diseases of the blood-forming organs.

3. *Granular Degeneration.*—This is a peculiar granulated appearance that the red blood cells take when they are stained with a variety of dyes. Ehrlich's hæmatoxylin-eosin solution is especially suitable for the demonstration of this form of degeneration. It is observed in a great number of conditions which produce general degenerative changes in the blood, such as anæmia, leukæmia, chronic lead poisoning, malignant growths, and the various infections. It has recently been shown that in chronic lead poisoning this form of degeneration is present previous to the appearance of clinical symptoms, and its detection is valuable from both prophylactic and therapeutic standpoints. Much speculation has taken place in regard to the mode of formation of these granules. Some have held that they are of nuclear origin, but this is improbable, and it seems certain that they are minute portions of degenerated hæmoglobin. This is Grawitz's opinion.

Osmotic Relations of Erythrocytes and Serum.

Normally the osmotic relation between the erythrocytes and blood plasma is such that the red blood cells are preserved in their integrity and the hæmoglobin shows no tendency to pass into the plasma. Under these conditions the serum is said to be "hyperisotonic." Such hyperisotonia varies within certain limits, according to the different proportions of water present. This hyperisotonia of the blood plasma is a provision of nature against the dissolution of the red blood cells

in a fluid which is subject to great variation in the proportion of water which it contains. If the relation between the erythrocytes and plasma was isotonic—that is, exactly sufficient to prevent the dissolution of the former—very small variations in the amount of water present in the plasma would cause destruction of the red blood cells. The condition of hyperisotonia, therefore, renders necessary for the destruction of the erythrocytes very large variation in the amount of water present in the plasma, such as can occur only in pathological conditions. During the last few years the osmotic relations of the erythrocytes and plasma have been especially studied by Baumgarten. He regards the process of hæmolysis as mainly dependent upon these osmotic relations. A full consideration of his views will be found in the section on Serum.

Methods for Determining the Osmotic Relations of Erythrocytes and Plasma.—These are given in detail in Vol. VII.

Chemical Composition of the Erythrocytes.

Chemically the erythrocytes are principally composed of hæmoglobin with small amounts of a globulin-like albumin, phosphates of sodium, potassium, calcium, and magnesium, and chlorides of sodium and potassium.

Hæmoglobin forms about ninety per cent. of the constituents of the erythrocytes. It is approximately composed of ninety-six per cent. albumin and four per cent. of a pigment containing iron (hæmochromogen). Under normal conditions hæmoglobin occurs in two forms—oxyhæmoglobin and reduced hæmoglobin. The significance of these forms of hæmoglobin is well known and requires no further consideration here. Physiologically the amount of oxyhæmoglobin may be increased by the withdrawal of liquids from the diet. Pathologically a *relative* increase in the amount of oxyhæmoglobin may be met with in those diseases which are accompanied by the excretion of excessive amounts of water, notably diabetes. A pathological decrease in the amount of oxyhæmoglobin is encountered in a large number of diseases. Prominent among these are chlorosis, pernicious anæmia, and leukæmia.

Tests for Hæmoglobin.—A large number of apparatuses have been devised for estimating the amount of hæmoglobin present in the blood. Of these Fleischl's, Miescher's modification of Fleischl's instrument, and Oliver's hæmoglobinometer are to be recommended as the most reliable, and when properly used they give sufficiently accurate results. As the result of my experience I have come to the conclusion that most of the other forms of apparatus in use give uncertain results. It is to be especially emphasized that in using the instruments above mentioned the final figures to be taken are those obtained by averaging

fifteen to twenty separate readings from the same blood specimen. In this way the source of error incident to any hæmoglobin estimation may be very largely eradicated.

Color Index is that fraction whose numerator corresponds to the percentage of hæmoglobin and whose denominator corresponds to the percentage of red blood cells present, taking 5,000,000 as a standard. Under normal conditions this is $\frac{100}{100} = 1$. Supposing that upon examination the percentage of hæmoglobin is 60 per cent., and the number of erythrocytes is 3,500,000, which would be 70 per cent. The color index in such an instance would be $\frac{60}{70} = \frac{6}{7} = .8\frac{4}{7}$. A high color index is practically observed only in pernicious anæmia. When it is found, therefore, the existence of this disease should be strongly suspected.

Spectroscopic Examination of the Blood.—This subject has received full consideration in Vol. VII.

Estimation of Blood Iron.—This is best accomplished by the use of Jolles' ferrometer. This is manufactured by Reichert, and full instructions for its use are given with each set. A detailed description is therefore not necessary here. Recently Jolles has improved his ferrometer and made it more suitable for clinical use. He has named it the "clinical ferrometer."

Under pathological conditions hæmoglobin may enter into combination with certain substances, and thus there may be produced methæmoglobin, carbon-monoxide hæmoglobin, nitric-oxide hæmoglobin, hydrogen-sulphide hæmoglobin, and melanin.

Methæmoglobin is frequently present in the blood after the ingestion of certain drugs, as chlorate or permanganate of potassium, turpentine, antifebrin, etc. Also frequently after the inhalation of nitrite of amyl or ether. Its presence is to be determined by spectroscopic examination.

Carbon-monoxide Hæmoglobin is met with in cases of coal-gas poisoning. It imparts a bright cherry-red color to the blood. Its spectrum is very similar to that of oxyhæmoglobin, but is to be differentiated therefrom by the fact that the addition of a reducing substance does not change the spectrum to that of reduced hæmoglobin, as is the case with oxyhæmoglobin. The presence of carbon-monoxide hæmoglobin can also be demonstrated by the addition to the blood of a solution of sodium hydrate (specific gravity, 1.3), when a red color is produced. Normal blood under the same conditions gives a dirty brown color.

Nitric-oxide Hæmoglobin is found in the blood in cases of nitric-oxide poisoning. Its spectrum is practically the same as that of carbon-monoxide hæmoglobin, but the absorption bands are less marked.

Hydrogen-sulphide Hæmoglobin.—This substance is said to be pres-

Enumeration of Erythrocytes.—The enumeration of the red blood cells is best accomplished by the use of the Thoma-Zeiss apparatus, described in Vol. VII.

Blood Plates.

These are circular or oval bodies which are usually homogeneous but may be granular in appearance. In regard to their origin, three views have been advanced: 1. They are an early stage in the development of the erythrocytes. 2. They originate from the erythrocytes. 3. They originate from the nuclei of the leucocytes. The majority of observers agree that the second mode of origin is the most likely.

The exact *chemical composition* of the blood plates has not been definitely determined. Löwit holds that they are principally composed of globulin. Lilienfeld maintains that chemically they belong to the nucleo-albumins and hence contain phosphorus. Apparently they are not digested by pepsin.

The number of blood plates normally present in the blood has not been definitely determined, owing to the inaccuracy of the methods used therefor. The figures which have been given vary from 200,000 to 650,000 per cubic millimetre.

Nothing of practical importance is at present known concerning the physiology or pathology of the blood plates.

The blood plates are lightly stained by both acid and basic dyes.

Enumeration of Blood Plates.—Two methods are in general use: 1. Place a drop of Hayem's fluid (see Vol. VII., p. 266) upon the finger and prick through this drop. Transfer the drop to the Thoma-Zeiss cell and examine.

2. *Brodie and Russell's Method.*—Count the red blood cells in the ordinary way. Place a drop of the following solution upon the finger and prick through it: Equal parts of a saturated solution of dahlia in glycerin and a two-per-cent. solution of sodium. In this solution by means of the Thoma-Zeiss apparatus estimate the proportion of blood plates to erythrocytes. The determination of the number of blood plates in 1 c.mm. of blood is then obtained by combining the results obtained in both of these observations. It is necessary that the second step of this method be quickly completed, as the solution employed soon destroys the erythrocytes.

Leucocytes.

Origin.—It must be confessed that the origin of the leucocytes in embryonal life has not at the present time been definitely determined, notwithstanding the vast amount of experimental research that has been conducted along these lines during the past few years. Three

views are existent in regard to their original formation: (1) That they develop from the primary wandering cells of mesodermal origin; (2) that they arise from the capillary endothelium; (3) that they are derivatives of the epithelial cells, principally of the intestine. The first of these theories has been especially evolved by Saxer and Ziegler, and is to-day accepted by the majority of histologists. The question of the common origin of the red and white blood cells has been much discussed. It seems certain that in the embryo such exists and that both of these varieties of cells arise from the primary wandering cell above mentioned. After birth, however, and probably also in late fœtal life, these primary wandering cells cease to exist, and it may be regarded as definitely settled that in adult life the erythrocytes and leucocytes have an entirely independent origin. Once having been formed, the leucocytes multiply exclusively by karyokinesis. The locations of the origin of leucocytes in the embryo are the loose connective tissue of various regions and the liver. The first-named location is that in which the leucocytes first appear. Very soon, however, they make their appearance in the liver, being found in the lymph and blood capillaries, in the interstices of the connective tissue, and between the liver cells. For a time the liver becomes the chief site of their formation. Somewhat later in fœtal life the formation of leucocytes is gradually transferred from the liver to the lymphoid and adenoid structures. In adult life under normal conditions the location of the reproduction or multiplication of leucocytes is strictly limited to the lymphoid tissues, including the lymph nodes, spleen, and bone marrow.

Origin of the Various Forms of Leucocytes.—In early fœtal life the lymphocyte is the sole variety of leucocytes present. In late fœtal life the other varieties of leucocytes begin to make their appearance, and at birth all the forms of leucocytes seen in adult life are present. While it is true that the leucocytes in general in fœtal life have a common origin from the primary wandering cell, as above noted, it does not necessarily follow that subsequently in adult life the different varieties of leucocytes form links in a continuous chain and that here all forms originate from the lymphocyte. The origin of the different varieties of leucocytes will be considered under their respective descriptions.

Chemistry of Leucocytes.—With regard to the chemical composition of the leucocytes, no new facts worthy of especial enumeration have been developed since 1897.

Finer Structure of Leucocytes.—The protoplasm of the small and large mononuclear leucocytes shows the reticulated structure of ordinary protoplasm. Any granules normally present in them are made up of fine nodal thickenings of this reticulum. In neutrophilic and

eosinophilic leucocytes the granules are connected by threads with the reticulum, and are hence integral parts of the same.

Significance of the Cell Granules.—Recent investigations have shown that the cell granules are secretory in character and represent the centre of the specific functions of these cells. The precise nature of this secretory function has not as yet been definitely determined. While it has been regarded by many as the essential factor in the production of bacterial and toxic immunity, it is by no means satisfactorily established that such is the case, especially in the light of the recent exhaustive theory of immunity advanced by Ehrlich.

Degeneration of Leucocytes.—The degeneration of leucocytes may be either acute or chronic in character.

1. *Acute Degeneration.*—This is especially prominent in connection with the acute infectious diseases. The protoplasmic granules of the neutrophilic and eosinophilic leucocytes are frequently reduced in number and fail to stain characteristically. The reticulum of the small and large mononuclear leucocytes becomes coarser and even distinctly granular. The nuclei of all leucocytes undergoing acute degeneration stain faintly with the basic dyes and possess a shrunken appearance.

2. *Chronic Degeneration.*—This is seen in chronic diseases accompanied by hyperleucocytosis and is particularly frequent in leukæmia. It is characterized by a reduction in the number of granules and by the presence of vacuoles and droplets of glycogen. The nuclei are also faded and distorted, while frequently the cell bodies undergo fragmentation. Hydropic degeneration is frequently observed in certain chronic diseases, especially leukæmia and malaria.

Varieties of Leucocytes.—At the present time we differentiate ten varieties of leucocytes. The first six are present in varying proportions in normal blood, while the last four are observed only under pathological conditions. 1. Small mononuclear leucocytes (lymphocytes). 2. Large mononuclear leucocytes. 3. Transitional leucocytes. 4. Polymorphonuclear neutrophilic leucocytes. 5. Eosinophilic leucocytes. 6. Basophilic leucocytes. 7. Neutrophilic myelocytes. 8. Eosinophilic myelocytes. 9. Small neutrophilic pseudolymphocytes. 10. Irritation forms.

1. *Small Mononuclear Leucocytes* (*Lymphocytes*).—This variety of leucocytes is practically formed only in the lymph glands. They are about the size of a red blood cell, but may be slightly smaller or larger than this. Both the nucleus and protoplasm take up only basophilic dyes and show no affinity for acid or neutral stains. Often the protoplasm shows a greater avidity for the basophilic dye than does the nucleus, so that the former is the more intensely stained. The nucleus frequently shows the presence of one or more nucleoli. Under nor-

mal conditions lymphocytes constitute from twenty-two to twenty-five per cent. of the total number of leucocytes. Pathologically their greatest absolute and relative increase is seen in lymphatic leukæmia. A relative increase is found in healthy infants, in certain infantile diseases, particularly those affecting the gastrointestinal tract, in chlorosis, in pernicious anæmia, in secondary syphilis, in the latter days of typhoid fever, in some cases of Basedow's disease, in hæmophilia, and in goitre.

2 and 3. *Large Mononuclear and Transitional Leucocytes.*—In regard to the origin of large mononuclear leucocytes, there are at present two views. The first is that they represent a later stage in the development of the lymphocyte. The second, maintained by Ehrlich, regards them as originating independently, principally in the bone marrow and probably to a slight extent also in the spleen. As our knowledge of the increase of these cells under pathological conditions widens, it seems probable that the latter view is correct. In size they vary greatly. Some of them are little larger than lymphocytes, while others are the largest cells encountered in normal blood. Both nucleus and protoplasm are basophilic as in the small mononuclear variety, but in contradistinction to these the protoplasm shows less affinity for these dyes than does the nucleus, so that the former is less intensely stained than the latter. It is important, however, to remember that different stains vary in their ability to bring out these characteristics. Ehrlich's triacid and Wright's stain produce the best differentiation between the nucleus and protoplasm of these large mononuclear leucocytes, and for this purpose the latter is to be preferred to the former. For the enumeration and study of this variety of leucocytes one of these stains should always be employed. In health these cells, together with the transitionals, constitute from two to four per cent. of the total number of leucocytes. They are increased in number in chronic malaria, typhoid fever, measles, and the end of scarlet fever, in Addison's disease, and also in many of the conditions which show an increase in the small mononuclear forms. The transitional leucocytes develop directly from the large mononuclears, and are to be distinguished from these only by the fact that their nucleus is distinctly invaginated. Occasionally a few neutrophilic granules are seen in their protoplasm. As a rule, the nucleus of these transitional leucocytes takes a deeper tint with Ehrlich's triacid stain than does the nucleus of the large mononuclears.

4. *Polymorphonuclear Neutrophilic Leucocytes.*—The origin of these leucocytes is still a matter of much discussion. Three theories may be said to exist to-day upon this subject, each of which has its quota of adherents: (1) That advanced by Ehrlich, who maintains that they are exclusively derived from the neutrophilic myelocytes of the bone

marrow. (2) Ouskow's theory, which regards them exclusively as of lymphocyte origin. (3) Dominici's theory. This observer holds that these leucocytes are the final links in a chain the first links of which are lymphocytes, large mononuclear leucocytes, and neutrophilic myelocytes in the order named. According to this view the polymorphonuclear neutrophilics are not formed exclusively in the bone marrow, but may also arise in the spleen and lymph glands. Dominici, however, admits that under certain pathological conditions these cells may arise directly from the large mononuclear leucocytes without passing through the myelocytic stage. It is not possible at the present time definitely to say which of these views is correct, but it seems probable that the origin of these leucocytes is twofold—from both the neutrophilic myelocytes and the large mononuclear leucocytes. In size the polymorphonuclear neutrophilics are from two to three times as large as the erythrocytes. Their nucleus is polymorphonuclear, having the shape of an S, Z, or Y. At times the nucleus may be completely divided so as to form two or three distinct lobes. Their protoplasm shows the presence of the finest neutrophilic granules—the S-granulations of Ehrlich. The color of these granules varies with the stain employed, but they never take the eosin bright red stain and are always darker in appearance than the granules of the eosinophiles. The polymorphonuclear neutrophilics constitute from seventy to seventy-two per cent. of the total number of leucocytes. They form the vast majority of the so-called phagocytes, and in the various infective conditions they may be seen as such, one or more of the infecting microorganisms being contained within their protoplasm. The various forms of hyperleucocytosis due to infection are very largely due to an increase in the number of these cells. In certain pathological conditions they are relatively decreased in number. Among such conditions may be especially mentioned typhoid fever, also in the majority of instances they are *relatively* somewhat subnormal in number in myelogenous leukæmia.

5. *Eosinophilic Leucocytes.*—It may be regarded as practically certain that these leucocytes originate from the mononuclear eosinophilic cells (eosinophilic myelocytes) of the bone marrow. It is worthy of remembrance, however, that a few authors still maintain that they represent the senile stage in the development of the small mononuclear leucocytes. They vary in size from that of a small mononuclear leucocyte to that of a polymorphonuclear neutrophile. They are distinguished from this latter variety by the size and coloration of their protoplasmic granules when stained by a fluid containing eosin. These granules are distinctly larger than the neutrophilic granules and have an appreciable round form. Furthermore, with eosin they stain a bright red. In differentiating eosinophiles from neutrophiles Jen-

ner's stain gives better results than Ehrlich's for the beginner, although to one possessing a very little experience the latter stain is perfectly satisfactory for this purpose. As a rule, their nucleus is more distinctly divided and stains a brighter blue than does the nucleus of the neutrophiles. Normally the eosinophilic leucocytes constitute from two to four per cent. of the total number of leucocytes. A study of the increase in the number of eosinophiles (*eosinophilia*) has during the past few years attracted the attention of a large number of observers. As the result of this work we now know that in myelogenous leukæmia an absolute increase in the number of these cells is always present, and that the diagnosis of this disease may be negative if such is not the case, but that a relative increase in their number may or may not be found. An increase (relative or absolute) in the number of eosinophiles also occurs in bronchial asthma, certain bone diseases, skin diseases, nervous diseases, in helminthiasis, in trichinosis, diseases caused by intestinal parasites, gonorrhœa, malignant neoplasms, and in the post-febrile stage of infectious diseases. A decrease in their number is observed in pneumonia and during the course of most infectious diseases. Recent investigations have brought out the interesting fact that in the eruptive stage of scarlet fever there is present an absolute as well as a relative increase in the number of eosinophiles. In this respect scarlet fever apparently stands unique among the acute exanthemata. The eosinophiles are phagocytic in character.

The origin and significance of eosinophilia have been variously interpreted by different observers. According to Neusser, the sympathetic nervous system regulates the supply of eosinophiles to the blood, and eosinophilia is dependent upon causes which impair this nervous mechanism. As a matter of fact, at the present time we do not know why in certain infectious and systemic conditions the eosinophiles are increased in the peripheral blood, while in other infectious and systemic conditions they are reduced in number or absent. We know, however, that eosinophiles are phagocytic cells, and the most reasonable explanation of eosinophilia which can be advanced at the present time is that there are certain substances, of microbic or other origin, which when introduced into the body call forth an increase in the number of eosinophilic leucocytes in the peripheral blood. By what mechanism such an increase is brought about we are in our present knowledge totally unable to state.

6. *Basophilic Leucocytes* (*Mast Cells*).—The origin of this variety of leucocytes is not clear. They are characterized by the presence in their protoplasm of granules, as a rule larger than those of the eosinophiles, which show an affinity only for the basic dyes, but stain metachromatically with these. Often these granules are fewer in number than those present in the neutrophiles or eosinophiles. With Jenner's

stain—which in the writer's opinion is the best for their demonstration—they take a violet color and are very characteristic in appearance. Ehrlich's triacid stain does not color these granulations. Wright's stain effectively colors them, but does not give so satisfactory pictures as Jenner's stain. The nucleus of these leucocytes is mononuclear. Mast cells are only occasionally seen in normal blood, but they may constitute 0.5 per cent. of the total number of leucocytes without having any pathological significance. Their greatest relative as well as absolute increase occurs in myelogenous leukæmia, and their presence in abundance may be considered diagnostic of this disease. Recent investigations and the extensive employment of Jenner's stain have shown that basophilic leucocytes are frequently present in moderately increased numbers in a variety of other conditions, especially in conjunction with eosinophilia, and that such increase may be either relative or absolute or both.

7 and 8. *Myelocytes* (*Neutrophilic and Eosinophilic*).—The majority of recent investigators agree with Ehrlich that these cells originate exclusively in the bone marrow and are the young forms of the polymorphonuclear neutrophilic and eosinophilic leucocytes respectively. A few, however, maintain that they represent a later stage in the development of the small mononuclear leucocytes (see section on polymorphonuclear neutrophilic leucocytes). They respectively correspond to the descriptions given for the polymorphonuclear neutrophilic and eosinophilic leucocytes, except that they are mononuclear and their nucleus possesses only a feeble affinity for dyes. They are never found in normal blood. According to some observers neutrophilic myelocytes should be divided into two classes on the basis of their size: (1) Medium sized. These are seen in many diseased conditions, but principally in leukæmia and secondary anæmia. (2) Large sized. Found practically exclusively in myelogenous leukæmia and v. Jaksch's anæmia. Eosinophilic myelocytes, according to the same observers, are to be divided into two classes in accordance with the *size of their granules:* (1) Those in which the granules are the same size as those seen in eosinophilic leucocytes. These are found abundantly in myelogenous leukæmia, less frequently in v. Jaksch's anæmia, sometimes in myxœdema, in some infectious diseases, and in pernicious malaria. (2) Those in which the granules are of excessive size. These forms are supposed to be pathognomonic of myelogenous leukæmia. In addition to the above diseases myelocytes (neutrophilic and eosinophilic) of various characteristics have been observed in malignant growths with metastases in the bone marrow, severe posthemorrhagic anæmia, mercurial poisoning, scrofula, and in pneumonia following the crisis. Their exact pathological significance is not as yet absolutely determined, but in our present knowledge we are bound

to assume that their presence in the peripheral blood in fair amount denotes the existence of serious lesions of the blood-forming centres.

9. *Small Neutrophilic Pseudo-lymphocytes.*—These forms are supposed to be derived from the polymorphonuclear neutrophilic leucocytes by direct division, but whether this is so or not has not been as yet definitely determined. They are the size of the small mononuclear leucocytes. They correspond in general to the description given for the neutrophilic myelocytes, but are to be differentiated from these by their smaller size and their more deeply stained nucleus. They are never found in normal blood. They were first described by Ehrlich as seen by him in the blood of a case of hemorrhagic smallpox. In our present knowledge the demonstration of the presence of these leucocytes possesses no definite diagnostic or prognostic value.

10. *Irritation Leucocytes.*—The origin of these leucocytes is unknown. They are mononuclear, non-granular cells, which stain a rich brown with Ehrlich's triacid mixture. The nucleus is round and of a bluish-green color. They are not found in normal blood, but are believed to be present under the same conditions as myelocytes.

Neusser's Perinuclear Basophilic Granules.—These are basophilic granules often seen in and about the nucleus in mononuclear and polynuclear leucocytes. Neusser regards them as evidence of the so-called uric-acid diathesis and of favorable prognostic omen in tuberculosis. Recent investigations have shown, however, that this view is entirely erroneous. All who have had any considerable experience in the examination of stained blood specimens will agree that it is rare to examine a stained smear without detecting the presence of these granules. It is certain that either their presence or absence is of no significance. It is highly probable that they are merely artifacts.

ENUMERATION OF LEUCOCYTES.—The enumeration of leucocytes may be divided into: (1) Total enumeration; (2) differential enumeration. At the present day no leucocyte count is complete unless both of these factors are considered, and he who contents himself with a total enumeration in any given case fails in a great measure to realize the benefit to be derived from this work.

1. *Total Enumeration.*—During the last few years no new method has been devised which equals in accuracy that obtained by the use of the Thoma-Zeiss apparatus described in Vol. VII.

2. *Differential Count.*—The differential count of the leucocytes can be made only by the utilization of dried smears which have been subjected to some stain which differentiates the different varieties of leucocytes. *Technique:* The accuracy of the count very largely depends upon the character of the blood smear upon which it is made. The essential characteristics of a satisfactory smear are that it should be thin and evenly spread. Only in such are the leucocytes sufficiently

isolated from the red cells so that they are readily seen and characteristically stained. No differential count for diagnostic or prognostic purposes should be made upon smears in which the red blood cells and leucocytes are thickly massed together, as thereby inaccurate figures are frequently obtained and erroneous deductions drawn therefrom. Of the force of this statement I have frequently convinced myself by comparative tests. In making the smears two methods are of service: (1) Making smears upon glass slides. Here a drop of the blood is placed upon one end of the slide and smeared across it parallel with its long diameter by means of a bevel-edged slide or piece of glass. In making such a smear the pressure should be slight and constant, otherwise a poor smear will result. (2) Making the smears upon cover glasses. In this method the drop of blood is received on the centre of a perfectly clean cover glass. Upon this is then placed another cover glass, in such a manner that its angles will correspond to the sides of the first cover glass. These are now pulled apart by the fingers, using slight pressure. Thus a smear is obtained upon each cover glass. *Fixing:* In using most of the stains now in use, except Jenner's and Wright's, the blood smear must be fixed before it is subjected to the staining fluid. This is best accomplished by heat at 100°–120° C. for two minutes. If such is not used either of the following methods may be employed: Immersion in absolute alcohol for five to thirty minutes, equal parts of absolute alcohol and ether for two hours, one-per-cent. alcoholic solution of formol for one minute, by exposing to the vapor of twenty-five-per-cent. formalin for five minutes, or two-per-cent. osmic acid for two minutes. *Staining Fluids:* The principal differential stains which are in use to-day and which suffice for all purposes are Ehrlich's, Jenner's, and Wright's.

1. *Ehrlich's.*—Is described in Vol. VII.

2. *Jenner's.*—Prepared as follows: Equal parts of 1.2–1.25-per-cent. aqueous solution of Grübler's eosin (yellow shade) and of a one-per-cent. aqueous solution of methylene blue are mixed in an open basin, thoroughly stirred, and set aside for twenty-four hours. The mixture is then filtered through paper, washed in water, and dried; the washing process and drying are repeated. Of this dried precipitate a 0.5-per-cent. solution is made in pure methyl alcohol and ten-per-cent. glycerin added. No *fixing* of the smears is necessary when this stain is used. The smears should be immersed in this stain for from one to three minutes. The former time uniformly gives better results than the latter. Three points are essential to success in using this stain: (1) It is *absolutely* necessary that the smears be thin. (2) During the staining the slide or cover glass immersed in the stain must be covered; otherwise the methyl alcohol will evaporate and leave the dry precipitate upon the preparation, from which it cannot be washed off. (3)

At the expiration of the time the smear must be *actively* washed in water until the smear appears of a pinkish color. (4) The smear must be left to dry in the open air and not dried between filter paper. By following closely the above directions a good specimen may be uniformly obtained. The picture given by Jenner's stain is as follows: The red blood cells are terracotta, the nuclei of the leucocytes are blue, the plaques mauve, the neutrophilic granules a purplish-red, the eosinophilic granules a bright red, and the basophilic granules a dark violet. Malarial organisms and bacteria are stained blue. The chromatin bodies of the malarial parasites are not stained. The basophilic granules present in the granular degeneration of the red cells are stained blue. In the red blood cells undergoing polychromatophilic degeneration, the color gradually changes from a terracotta to a blue. Jenner's stain does not keep indefinitely, and it is necessary to test it from time to time in order to be sure that a correct picture is being obtained.

Wright's Stain.—Very recently James H. Wright has devised a new stain which is apparently superior to Jenner's in that it keeps indefinitely and gives a more complete picture. It gives a differential stain for the chromatin and cytoplasm of the malarial parasite. It also sharply differentiates the nuclei of the cytoplasm of the small and large mononuclear leucocytes. It further differentiates the granulations of the leucocytes in general. It is prepared as follows: To one-half-per-cent. aqueous solution of sodium bicarbonate is added one per cent. of methylene blue (Grübler's). This is heated for one hour in a cotton-plugged flask in an Arnold steam sterilizer, counting from the time "steam is up." All the bicarbonate should be thoroughly dissolved before the methylene blue is added. The mixture is then removed from the sterilizer and allowed to cool. It is then poured without filtering into a large open dish, and amid constant stirring a 1:1,000 aqueous solution of eosin (Grübler's yellow shade) is added until the blue color becomes purple and a yellowish scum of a metallic lustre forms on the surface. It is then filtered through paper and the precipitate allowed to dry thereon. The dye thus obtained is added to pure methylic alcohol to saturation. This saturated alcoholic solution is then filtered and to the filtrate is added twenty-five per cent. of methylic alcohol. This is the staining fluid. The technique in using this stain is as follows: (1) Cover the preparation without previous fixation with the staining fluid for one minute. (2) Add to the stain on the preparation water drop by drop until the mixture becomes semi-translucent and a yellowish metallic scum forms on the surface. Allow this to remain on the preparation for two or three minutes. (3) Wash in water until the smear has a yellowish or pinkish tinge on its thinner or better spread portions. (4) Dry between filter paper and mount

in balsam. The picture given by this stain is as follows: The small mononuclears show a dark purplish-blue nucleus and a robin's egg blue cytoplasm; the large mononuclears have a blue or lilac colored nucleus, and the cytoplasm is pale blue or dark lilac. They may show dark lilac or deep purple colored granules, which are not so numerous as the granules in the neutrophilics; the neutrophilics have a dark blue or dark lilac colored nucleus and granules of a reddish-lilac color; the eosinophiles have a blue or dark lilac colored nucleus and granules of a bright red embedded in a cytoplasm which has a blue color; the basophilics have a purplish or dark blue stained nucleus and a light blue cytoplasm in which are embedded coarse spherical granules of a dark blue or dark purple color, which may be at times almost black; the red blood cells are orange or pink in color, and in granular degeneration the granulations are well brought out. Nucleated red blood cells have a deep blue nucleus. The body of the malarial parasites is blue, while the color of the chromatin bodies varies from a lilac color through shades of red to almost black. There is no doubt but that this stain when properly carried out gives a picture which exceeds that given by any other method. From a limited experience with its use I regard it, all in all, as the most satisfactory yet devised. It must be confessed, however, that the picture above described is not always accurately obtained, at least until one has had a fair amount of experience in the use of the method. It is hardly probable, however, that even a beginner would fail perfectly to differentiate the varieties of leucocytes present. As it is very easy of manufacture and apparently indefinitely retains its original properties, the writer believes that its extended use is assured.

In making differential stains for diagnostic purposes certain precautions must be taken in order that trustworthy results may be obtained; (1) At least one thousand leucocytes should be counted. It is better that this number be two thousand. (2) One-half of these should be stained by Ehrlich's triacid stain and the other half either by Jenner's or Wright's stain. Especially should it be noted that no count should ever be considered valid in which either Jenner's or Wright's stain has not been used. (3) While a microscopical mechanical stage is not an absolute necessity, it is nevertheless true that for careful work its use cannot be dispensed with.

Iodophilia.—Iodophilia is the staining reaction which certain of the white cells of the blood show when a dried blood film is brought into contact with the following solution: Iodine 1 gm., potassium iodide 3 gm., water 100 c.c., gum arabic 50 gm. The use of this mixture was first suggested by Ehrlich in 1883. It has not, however, come into use as a means of clinical diagnosis and is but infrequently used at the present day. In this reaction the red blood cells are uniformly colored

a bright yellow, while the white cells are stained a lighter tint, the nucleus being somewhat more refractile and lighter than the cytoplasm. In certain pathological conditions the uniform coloration in the protoplasm of the polymorphonuclear neutrophilics is broken by the appearance of reddish-brown granules. Small and large masses outside of the corpuscles similarly stained are also seen. This is iodophilia, and we thus differentiate an (1) extracellular and (2) intracellular reaction. The recent investigations of Locke and Cabot, while not entirely conclusive, have shown that considerable importance attaches to the intracellular reaction, while none is to be ascribed to the extracellular. They regard the presence of this intracellular reaction as a pathological phenomenon, and have never met with it in the blood of normal individuals. They do not regard it as a special disease or condition, but as evidence of a general toxæmia. Though more constantly encountered in the presence of pus, a diagnosis of sepsis cannot be made from the reaction alone. They do not find that iodophilia coincides with any of the ordinary physical signs, as leucocytosis or fever. They have never found it in any but severe cases, and regard it as a more reliable sign than either leucocytosis or fever. A positive reaction occurs with fair regularity in the following conditions: Infection with pyogenic organisms, whether local or general; toxæmia of bacterial origin, as diphtheria and typhoid fever; non-bacterial toxæmia (uræmia), disturbances of respiration, and grave anæmia, both primary and secondary. These observers have not found a positive reaction in pleurisy, rheumatism, extra-uterine pregnancy, alcoholism, abscesses with free drainage, lead poisoning, early malignant disease, nervous conditions, or pure tuberculous infection. More observation is required before the diagnostic and prognostic value of this reaction can be definitely determined. At present we can regard it only as an auxiliary sign of greater or lesser significance.

Leucocytosis.

Strictly speaking, the term leucocytosis means an increase in the number of leucocytes. It has, however, been customary to consider under leucocytosis those conditions in which either an increase or a decrease in the number of leucocytes takes place. For this reason we speak of hyperleucocytosis and hypoleucocytosis. In view of this and to avoid confusion, it is best when considering a variation in the number of leucocytes to use one of the two latter terms and in so far as possible to discontinue the use of the word "leucocytosis." Under normal conditions the number of leucocytes per cubic millimetre may vary between four thousand and ten thousand. It seems certain that figures outside of these limits indicate the presence of pathological phenomena.

Hyperleucocytosis.

An increase in the number of leucocytes may be either physiological or pathological.

Physiological Hyperleucocytosis.

Physiological hyperleucocytosis occurs in infancy and childhood, as the result of the process of digestion, exercise, or cold bathing, and in pregnancy. First of all, it is important to remember that in physiological hyperleucocytosis the different varieties of leucocytes are increased in like ratio, so that while the total number of leucocytes is increased the percentage relations between the different varieties remain normal. This is the cardinal difference between physiological and pathological hyperleucocytosis. This fact, to a certain extent, reduces the value of the total leucocyte count in estimating a pathological hyperleucocytosis and enhances the value of the differential leucocyte count for this purpose. While it is true that a high total leucocyte count when taken into consideration with clinical symptoms as a rule means that the hyperleucocytosis is pathological, it is equally true on the other hand that a differential leucocyte count frequently demonstrates the presence of a pathological hyperleucocytosis when the total count is not significantly raised above the normal. Especially is this true in the early days of infective processes which produce a hyperleucocytosis. A detailed description of the various forms of physiological hyperleucocytosis above noted is to be found in Vol. VII. of this work.

Pathological Hyperleucocytosis.

Pathological hyperleucocytosis may be active or passive. In *active pathological hyperleucocytosis* the phagocytic elements play the chief rôle. It is subdivided into (1) polynuclear hyperleucocytosis, in which the polymorphonuclear leucocytes or eosinophiles (see section on Eosinophiles) are principally concerned; and (2) mixed hyperleucocytosis, in which, in addition to the appearances present in polynuclear hyperleucocytosis, myelocytes (both neutrophilic and eosinophilic) are present.

In *passive pathological hyperleucocytosis* the hyperleucocytosis is dependent upon an increase in the number of lymphocytes.

Pathological hyperleucocytosis occurs under a variety of conditions, as follows: 1. As the result of microbic infection—so-called inflammatory or toxic hyperleucocytosis. 2. As the result of diseases of the blood-forming organs. 3. In association with malignant growths. 4.

As the result of hemorrhage. 5. Ante mortem. 6. Following the administration of certain drugs.

1. *As the Result of Microbic Infection or Toxæmia.*—This form of pathological hyperleucocytosis is *active.* The polymorphonuclear neutrophilics are both relatively and absolutely increased in number. Usually the number of eosinophiles is relatively decreased, but in the majority of cases absolutely increased. In some instances, however, the eosinophiles are both relatively and absolutely increased (for a consideration of these, see section on Eosinophiles). The small and large mononuclear leucocytes and transitionals are increased absolutely but not relatively in number. No leucocytes which are not normally found in the blood are present. This form of pathological hyperleucocytosis is observed in all infectious processes with the exception of typhoid fever, pure tuberculosis, measles, and probably influenza. The hyperleucocytosis which accompanies gout, acute yellow atrophy of the liver, acute and chronic nephritis, cirrhosis of the liver, hydronephrosis, and acute gastro-intestinal disorders is regarded by most authors as toxic or, more properly, autotoxic in origin, and comes within this classification. Much speculation has been indulged in with respect to the significance of this form of hyperleucocytosis, and many views appertaining thereto have been advanced. Its exact mode of production has not as yet been definitely determined, and a consideration of the various theories relating thereto can at the present time lead to no satisfactory conclusions. All, however, agree that this form of hyperleucocytosis is one of the defensive phenomena which the body exerts in its fight against infection and intoxication. Metchnikoff was the first to draw attention to this fact in the development of his theory of phagocytosis. It has always been and is now considered by him the chief factor in the production of both bacterial and toxic immunity. Recent investigations, especially those of Ehrlich and Bordet, have, however, conclusively shown that it is but one of several phenomena which are operative in the production of immunity. Nevertheless it seems certain that, if in those cases of infection and intoxication which should show a hyperleucocytosis the same is absent, the body is materially if not fatally weakened in its power to bring about an immunity. In any given case the intensity of the hyperleucocytosis depends upon two factors: (1) The virulence of the infecting agent, and (2) the inherent capability of the body to respond to the call for protection. Only in those instances, therefore, in which the first of these factors can be determined is it possible to draw from the intensity of the hyperleucocytosis present legitimate prognostic conclusions as to the power of the body to bring about an immunity. Thus in any given case a slight hyperleucocytosis may mean an infection with a slightly virulent microorganism from which the body is

abundantly able to protect itself, or an infection with a very virulent organism which has overpowered the body in its attempts at protection. On the other hand, an intense hyperleucocytosis in any given case may mean an infection with a slightly virulent organism in a body which markedly reacts to a weak infecting agent, or it may mean an infection with a very virulent microorganism against which a body of moderate protective ability is endeavoring to cope. Recently much has been written in regard to the value of the leucocyte count as a prognostic and therapeutic indicator in various infections, especially those which are commonly called septic. Particularly has it been heralded as of great importance in the operative treatment of appendicitis. As observations along this line increase it becomes apparent that the great value accredited to it in this respect in many quarters is to lose ground. This form of hyperleucocytosis is not a symptom; it is a process dependent upon certain factors. If one of these factors (the virulence of the infecting organism) is left out of consideration, it is certain that erroneous conclusions may be drawn. It is certain that in the future the mere enumeration of the leucocytes in a given infection will not be considered a satisfactory basis on which to found therapeutic measures or prognostications.

2. *As the Result of Diseases of the Blood-forming Organs.*—This form of hyperleucocytosis may be active or passive. Its various forms will be considered under the various diseases of these organs.

3. *In Association with Malignant Growths.*—A considerable number of cases of carcinoma show an active leucocytosis, and this is usually polymorphonuclear neutrophilic in character. In sarcoma a hyperleucocytosis is occasionally met with, and in such cases the eosinophiles and lymphocytes play the chief rôle. It must be remembered, however, that the presence or character of a hyperleucocytosis, while it may be of some value, is in doubtful cases not sufficient to establish a differential diagnosis between carcinoma and sarcoma. The same may be said in regard to gastric ulcer and carcinoma of the stomach.

4. *As the Result of Hemorrhage.*—The hyperleucocytosis which follows hemorrhage may be active or passive, and usually varies directly in intensity with the quantity of blood lost.

5. *Ante Mortem.*—An increase in the number of leucocytes just before death has been observed by several authors in connection with diseases in which no hyperleucocytosis was previously present. Its mode of origin and significance are not at present understood. In certain diseases of the blood-forming organs, as leukæmia, an ante-mortem hyperleucocytosis is frequently observed. In these cases the character of the hyperleucocytosis is similar to that which was previously present.

6. *Following the Administration of Certain Drugs.*—An active hyperleucocytosis affecting principally the polymorphonuclear neutrophilics

is observed in cases of poisoning with potassium chlorate, arsenic, and illuminating gas. Also in some persons following the administration of atropine, quinine, and the prolonged administration of chloroform or ether. It is probable that here the hyperleucocytosis is of the same significance as that due to microbic infection.

Hypoleucocytosis.

A reduction in the number of leucocytes below that normally present is always pathological in character. No physiological hypoleucocytosis has been observed. Hypoleucocytosis may be present under the following conditions: 1. As the regular accompaniment of certain infections. 2. Under certain conditions in those infections which regularly show a hyperleucocytosis. 3. In certain cases of anæmia and pseudoleukæmia. 4. As the result of the ingestion of certain drugs.

1. *As the Regular Accompaniment of Certain Infections.*—As stated above, typhoid fever, tuberculosis, influenza, and measles are regularly accompanied by a decrease in the number of leucocytes normally present. It should, however, be remembered that this statement holds true so far as the first three of these diseases are concerned only when the symptoms present are due to a pure infection with the bacillus typhosus, bacillus tuberculosis, and influenza bacillus respectively. Cases of typhoid fever, tuberculosis, and influenza, in which a mixed infection is present, regularly show a *hyperleucocytosis.* In recent years much attention has been given to the hypoleucocytosis which regularly accompanies pure typhoid infection. Here the polymorphonuclear neutrophiles are the leucocytes which suffer the greatest reduction in number both relatively and absolutely. Furthermore, while the large mononuclear leucocytes are in most cases *absolutely decreased* in number, they are always *relatively increased* in number. The characteristic leucocyte count of pure typhoid infection is one which gives (1) a total reduction in the number of leucocytes, (2) a relative and absolute reduction in the number of polymorphonuclear neutrophilics, and (3) a *relative increase* in the number of large mononuclears. The relative number of small mononuclears remains about normal, while the absolute number is usually decreased. My own experience with the leucocyte count (total and differential) as an aid in the diagnosis of typhoid fever has been most satisfactory. In those cases which have recently come under my observation the characteristic leucocyte condition has been established early in the disease, always within the first clinical week, and has thus been of great aid in the early detection of this disease. It is not to be asserted that all cases of clinical typhoid fever show this condition early or at any time

during the disease, for we now know that in many cases of this disease a mixed bacterial infection is present very early in its course, if indeed it is not operative from the inception of the fever. In such cases it is not logical to suppose that the characteristic leucocyte condition of pure typhoid infection would be found. The absence of the characteristic leucocyte count, therefore, in no way negatives a diagnosis of clinical typhoid fever, but it is very probable that it does negative a diagnosis of pure typhoid infection. However, from a number of comparative observations which I have recently made I believe that in clinical typhoid fever a characteristic leucocyte count is more often obtained early in the disease (within the first week) than is a positive Widal reaction, and as an aid in the early diagnosis of this disease I place it above the latter test. I have never seen a case which gave a characteristic leucocyte count in the first week which did not subsequently prove to be typhoid fever. On the other hand, I have seen cases which failed to give a characteristic count eventually prove to be typhoid. The hypoleucocytosis which accompanies tuberculosis is quite rarely met with in pulmonary tuberculosis, for the reason that when such cases are first seen a mixed infection is usually present. It has no peculiar characteristics. Authors differ as to the existence of a hypoleucocytosis in influenza. This is probably due to the fact that the bacteriological basis of this disease is not as yet definitely settled. It seems certain that in those cases in which Pfeiffer's bacillus is found hypoleucocytosis is usually present. Notwithstanding our indefinite knowledge in regard to the bacteriology of measles, it is certain that a hypoleucocytosis is generally present in this disease. It, however, has no peculiar differential characteristics.

2. *Under Certain Conditions in Those Infections which Regularly Show a Hyperleucocytosis.*—A hypoleucocytosis is met with in certain infections which regularly show a hyperleucocytosis when the power of the body to resist such an infection is or subsequently becomes slight. Under such conditions, therefore, the presence of a hypoleucocytosis is a prognostic sign of unfavorable omen.

3. *In Certain Cases of Anæmia and Pseudoleukæmia.*—In certain severe cases of anæmia a hypoleucocytosis supervenes. It has no especial characteristics and is always of unfavorable omen, as it indicates an inability of the bone marrow to produce blood corpuscles. The same may be said of pseudoleukæmia.

4. *As the Result of the Ingestion of Certain Drugs.*—A hypoleucocytosis is frequently observed after the ingestion of camphoric acid, picrotoxin, sulphonal, trional, agaricin, tannic acid, and menthol. The significance of such a hypoleucocytosis is not understood and but little if anything is known of its peculiar characteristics.

Leukæmia.

ETIOLOGY.—During the last few years considerable attention has been devoted to the etiology of leukæmia. Especial mention is to be made of the experimental research which has been conducted along this line by various observers. Nevertheless it cannot be said that material knowledge has been gained thereby in regard to the origin of this disease and its ultimate causative factors. Löwit has strenuously endeavored to demonstrate the infectious nature of leukæmia and claims to have been successful therein. He maintains that this disease is caused by a protozoon, the presence of which he has been able to demonstrate in the blood of leukæmic patients. In such blood these microorganisms may be found within the leucocytes or free in the plasma. Furthermore, he claims that by inoculating leukæmic blood or an emulsion of leukæmic tissues (spleen and bone marrow) into rabbits and guinea-pigs, a fatal pathological condition is inaugurated in these animals which in many respects is similar to leukæmia, but which does not show the usual pathological lesions of this disease. Other observers have not been able to confirm in any considerable measure Löwit's results. While all admit that the bodies described by Löwit as protozoa are frequently observed in leukæmic blood, they hold that these are not microorganisms, but are either artifacts produced in the staining process or degenerated portions of the leucocytes. Türck has been especially outspoken in his condemnation of Löwit's views concerning the infectious origin of leukæmia. While it is true that the inoculation of rabbits and guinea-pigs with leukæmic blood frequently produces the death of these animals, the research of many investigators definitely proves that this result is not brought about by any one factor present in such blood, but may be due to a variety of causes. Thus many animals so inoculated die of a pure streptococcus septicæmia. It is certain that animals inoculated in this manner, whether they die or live, do not at any time show leukæmic changes in their organs or blood. It may be true that leukæmia is microbic in origin, but it is certain that the bodies described by Löwit are not the cause of this disease. On the other hand, considerable speculation has been indulged in with regard to the so-called neoplastic character of leukæmia. Kottmann, Herzfeld, and Gilbert regard it as a sarcoma of the lymphocytes. When we take into consideration the present knowlege of the origin of neoplastic growths in general, it is evident that such a conception of leukæmia in no way elucidates the etiology of this disease, but only further complicates the problem. In regard to the pathogenesis of leukæmia, it may be regarded as settled that it

is a primary disease of the blood-forming organs, involving principally the bone marrow and the lymphoid tissues. The exciting or predisposing causes of leukæmia have been extensively considered in Vol. VII. of this work. Exactly how far they are operative in bringing about its development cannot be determined until more knowledge is obtained with respect to its ultimate causation.

PATHOLOGICAL ANATOMY.—A few cases of leukæmia have been observed in which no pathological alterations have been found in the internal organs. In the majority of instances, however, such alterations are present and are more or less distinctive in character.

Bone Marrow.—The essential lesion of the bone marrow is a cellular hyperplasia affecting the leucocytes therein. This varies in character and is more or less pronounced according to the type of the disease. In the lymphatic form the lymphocytes alone are increased, and neutrophilic and eosinophilic cells are relatively few in number. Such an increase of lymphocytes may be marked or it may be very slight or even in some cases absent, so that in this form of leukæmia no alterations may be found in the bone marrow. Since, however, the changes in the bone marrow are focal and may be widely diffused throughout the osseous system, it is evident, as has been pointed out by Ewing, that extensive examination must be made with negative result before it can be assumed that bone-marrow lesions are absent in any given case. In myelogenous leukæmia the cells of the bone marrow which show the greatest increase in number are the neutrophilic myelocytes. Eosinophilic myelocytes are also present, but are not markedly increased in number. A combination of the characteristic bone-marrow lesions of lymphatic and myelogenous leukæmia are generally present, and pure types are rather infrequently observed. The erythrocytes of the bone marrow do not show much change in the early stages of leukæmia; as the disease advances, however, they undergo the same alterations as in pernicious anæmia, with the exception that megaloblasts are not so numerous. The macroscopic appearance of the bone marrow varies in acute and chronic cases. In acute cases it often strikingly resembles pus. In chronic cases it becomes fairly firm and lighter in color. In some cases various degenerative changes are observed.

Spleen.—In all forms of leukæmia the spleen is enlarged, but this is most marked in the lymphatic and lympho-medullary types. In pure myelogenous leukæmia the spleen is also constantly enlarged and in some cases greatly so, but in certain instances the enlargement is of such small extent that it can be demonstrated by physical examination with difficulty if at all. In lymphatic leukæmia this enlargement is at first due to a hyperplasia of the small and large mononuclear cells. Here the Malphigian bodies have been considered the

primary seat of the disease. In myelogenous leukæmia myelocytes, together with small and large mononuclear leucocytes, are present in the spleen. Ewing believes that in pure myelogenous leukæmia the primary enlargement of the spleen is due to the mechanical sifting of the red and white blood cells from the circulation and the inflammatory changes produced thereby. However this may be, in the later stages of all forms of leukæmia fibroid changes are present in the spleen, which commence in the trabeculæ and often extend throughout the pulp. Microscopical and chemical examination of the spleen emulsion gives the same characteristics as are encountered in the blood, with the exception that nucleated red blood cells are sometimes found in the former when they cannot be demonstrated in the latter. Also in myelogenous leukæmia myelocytes are much more abundant in the general circulation than in the spleen.

Lymph Glands and Structures.—No new facts in regard to the pathological lesions of the lymph glands and structures have been added since 1897.

The Blood.—The pathological changes in the blood have been extensively considered in Vol. VII., and will not be described *in toto* here, a few additional points only being mentioned. In the first stages of leukæmia the color index is subnormal, often being reduced to 0.4 or 0.5. In many cases it remains subnormal throughout the disease, but in others in the later stage the destruction of the red blood cells exceeds the reduction in the hæmoglobin, and the color index correspondingly rises and even in some cases eventually becomes hypernormal.

Myelocytes.—These may be either neutrophilic or eosinophilic. *Neutrophilic myelocytes* are of two varieties—small and large. The latter are provided with a pale eccentric nucleus and have been thought by some to be pathognomonic of leukæmia. It is, however, true that they are sometimes found in certain forms of secondary anæmia, although they are not so abundant as in leukæmia. Neutrophilic myelocytes are often met with in various stages of degeneration. The neutrophilic granules may be markedly reduced in number and in acute leukæmia may be entirely absent. Such neutrophilic myelocytes are to be differentiated from large mononuclear leucocytes only by the pallor of their nucleus. Neutrophilic pseudolymphocytes are sometimes observed. It should be remembered that while as a rule neutrophilic myelocytes are present in good number, yet there are certain cases of myelogenous leukæmia in which they are found only in small numbers, and that, moreover, they have been found in fair numbers in other conditions, especially diphtheria.

Eosinophilic myelocytes of various size and morphology are present. Certain forms in which the granules vary greatly in size and intensity

of stain are frequently observed, and are considered by Ewing to be pathognomonic of myelogenous leukæmia. It is doubtful whether such is the case, as certain observers have reported the existence of such myelocytes in other conditions, especially in pernicious malaria. Often a few basophilic granules are observed in the protoplasm of eosinophilic myelocytes.

Polynuclear Neutrophilic Leucocytes.—These are as a rule absolutely increased, but are generally relatively diminished in number in myelogenous leukæmia. In lymphatic leukæmia they are scarce and frequently entirely absent. They decrease relatively in proportion as the number of neutrophilic myelocytes increases. They show the same degenerative changes as do the neutrophilic myelocytes. Their nucleus usually stains faintly.

Eosinophiles.—In myelogenous leukæmia the eosinophiles are always absolutely increased in number, and if such is not the case the diagnosis of this disease may be abandoned. Their relative number may be normal or slightly increased. In lymphatic leukæmia they are few in number and may be entirely absent.

Small and Large Mononuclear Leucocytes.—The number of these leucocytes in leukæmia is subject to great variation. In all forms they are *absolutely* increased, the greatest absolute increase occurring in pure lymphatic leukæmia and the smallest absolute increase in the pure myelogenous variety. In lymphatic leukæmia they are always also relatively increased in number, while in myelogenous leukæmia they are frequently relatively diminished, but at times may be also relatively increased. Degenerative changes in these leucocytes are frequently observed.

Basophilic Leucocytes (*Mast Cells*).—As a rule the mast cells are increased in number in myelogenous leukæmia, but occasionally several examinations are necessary before their presence can be demonstrated. Recently attention has been called to the fact that the granules of the basophilic leucocytes of leukæmia are easily dissolved in water, and hence are frequently not detected with the employment of the ordinary staining methods in which water is employed to wash the dye from the specimen. It has been claimed that if water is entirely withheld from the specimen and alcohol is used for washing, a larger number of mast cells can be demonstrated in myelogenous leukæmia than with the use of former methods. More extended observation is necessary before it can be definitely said whether or not such is the case.

The pathological lesions found in the various organs and tissues of the body which are not considered in the foregoing have been described in Vol. VII. and do not call for reiteration here. Recent researches have added nothing that is materially new.

SYMPTOMATOLOGY.—*Types of Leukæmia.*—Two distinct types of leukæmia are observed—lymphatic and myelogenous. Either of these may be acute or chronic in its course, although acute myelogenous leukæmia is rare. The duration of acute leukæmia is from six weeks to three months. The chronic form may continue for three years. The designation "lymphatic leukæmia" should be reserved for those cases in which the small and large mononuclear leucocytes play the chief rôle in the leucocytosis and in which myelocytes and mast cells are infrequent. Myelogenous leukæmia should include those cases in which myelocytes, eosinophiles, and mast cells are fairly abundant, independent of the number of small and large mononuclear leucocytes.

As a rule the onset of leukæmia is insidious, although in acute cases it may be sudden. In the latter instances pronounced gastro-intestinal symptoms or hemorrhages, usually nasal, may usher in the attack. In chronic cases the first manifestations of the disease may be enlarged lymph glands, enlarged abdomen, marked dyspnœa, or palpitation.

Special Symptoms.—The special symptoms of leukæmia have been exhaustively considered in the original edition of this work. It should, however, be especially noted that the symptomatology of this disease is subject to great variation, with respect to both the intensity and character of the special symptoms, and that very often temporary improvement takes place. This should be particularly emphasized with respect to the leucocytosis of myelogenous leukæmia. In this form at times specimens of blood are obtained which show a very small number or even an entire absence of myelocytes and mast cells.

DIAGNOSIS.—The diagnosis of leukæmia is based solely upon an examination of the blood. It is true that in some cases of leukæmia the characteristic leucocytosis is not found. In such, a consideration of the clinical symptoms may authorize a *probable* diagnosis of leukæmia, provided that a leucocytosis of certain characteristics is present. A *positive* diagnosis of leukæmia may be made if there is present a total hyperleucocytosis of not less than 150,000, which shows (1) a fair number of myelocytes, mast cells, and an absolute increase of eosinophiles; or (2) an excessive number (eighty to ninety per cent.) of small and large mononuclear leucocytes. The absence, however, of such a characteristic hyperleucocytosis in no way negatives a diagnosis of leukæmia. A *probable* diagnosis of leukæmia may be made if characteristic clinical symptoms are present, combined with a hyperleucocytosis of 100,000 to 150,000, which shows (1) a small number of myelocytes and a slight absolute increase of eosinophiles; or (2) relative increase (fifty to eighty per cent.) of small and large mononuclear leucocytes. A diagnosis of myelogenous leukæmia may be negatived if an absolute increase of eosinophiles is not present. A diagnosis of

lymphatic leukæmia may be negatived if small and large mononuclear leucocytes are not relatively present in at least fifty per cent. In certain acute bacterial diseases, especially diphtheria and pneumonia, a hyperleucocytosis may be present which markedly resembles that of myelogenous leukæmia in that myelocytes (five to sixteen per cent.) are sometimes present. Here, however, the eosinophiles are rarely absolutely increased, and, furthermore, the clinical symptoms suffice to make the diagnosis clear. In secondary anæmia the hyperleucocytosis is not so marked as it is in leukæmia. There is never present as great an increase in small and large mononuclear leucocytes as would be necessary for a diagnosis of lymphatic leukæmia. It should be remembered, however, that a few cases of myelogenous leukæmia have been observed in which the total leucocytosis was slight and the number of myelocytes not over five per cent. until late in the disease. It is not possible to make an ante-mortem diagnosis in such cases. The characteristic hyperleucocytosis of leukæmia when present may be markedly altered by the occurrence of various complications. Acute infectious complications in leukæmia may transform the characteristic hyperleucocytosis so that it simulates in some respects an ordinary inflammatory leucocytosis. The effect of chronic infections upon leukæmic blood is much less marked than that of acute infections, and is rarely sufficient entirely to mask the characteristic hyperleucocytosis. In our present knowledge the early stages of leukæmia often escape detection even with the employment of the most careful blood examinations.

PROGNOSIS.—A few cases of leukæmia have been reported in which recovery has taken place, and it is evident that the disease is not of necessity fatal. Recoveries are, however, so rare that from a practical standpoint the prognosis is uniformly unfavorable. A fair proportion of leukæmic patients die from some intercurrent disease.

TREATMENT.—The last few years have seen no advances in the treatment of leukæmia. It has been thought by some that a marked temporary improvement can be brought about by the excessive administration of arsenic. Since temporary improvements are characteristic of this disease, especially so far as the blood condition is concerned, it is probable that the results obtained by the use of arsenic are delusionary. However, in our present knowledge it is probably the best treatment that can be instituted, and it should be immediately begun and pushed in all cases. Most leukæmia patients show a marked tolerance of this drug and ordinary doses do not suffice to produce its full physiological action. Heaton has reported a case in which two and two-third grains of arsenate of soda was taken without the appearance of poisonous symptoms. Fowler's solution is as good a preparation as any for this use. Its administration should be begun in

doses of three drops four times a day and rapidly increased until the first symptoms of poisoning are produced. The dosage thus attained should be continued so far as is compatible with the symptoms produced. Various tonic and hygienic measures as indicated should be instituted. Based upon the view that the spleen is the primary seat of the disease, various attempts have been made to reduce the size of this organ by electropuncture, galvanic electricity, etc. Such endeavors have been uniformly unsuccessful and are not to be recommended. Excision of the spleen has been performed forty-three times with five recoveries. While this operation is not generally recommended and from theoretical reasons seems to be contraindicated, it is nevertheless certain that it has given better results than any method of treatment now in use.

Pseudoleukæmia (Hodgkin's Disease).

ETIOLOGY AND PATHOGENESIS.—Since 1897 a considerable number of cases of so-called pseudoleukæmia have been reported. Many of these have been submitted to careful study and various deductions drawn therefrom. While as the result of this work it cannot be said at the present time that the etiology and pathogenesis of pseudoleukæmia are established, it is nevertheless true that our ideas with respect thereto have become somewhat more crystallized than they formerly were and that material ground has been gained in the ultimate solution of the problem. It is certain that on both clinical and pathological grounds the disease now known as pseudoleukæmia should be subdivided into two distinct types: (1) A febrile form characterized by the presence of a recurrent fever, in which the lymphatic lesions are tuberculous in type, but in which the bacillus tuberculosis may or may not be present. (2) A non-febrile form in which the lesions are sarcomatous in type and which never show the presence of the bacillus tuberculosis. The association of the bacillus tuberculosis with the first form of the disease has been pointed out by many observers; among these Sternberg should be especially mentioned. This author regards this form of pseudoleukæmia as essentially a tuberculosis of the blood-forming apparatus, and thinks that Hodgkin's disease in its entirety is tuberculous in origin. Others regard the presence of bacillus tuberculosis as merely accidental and as a complication engrafted upon a preëxisting pathological condition. Although it is possible that the latter view may be correct, its advocates have advanced no tangible proof thereof. In our present knowledge and with the almost uniform presence of tuberculous lesions and the bacillus tuberculosis in this form of pseudoleukæmia, we are forced to consider it essentially a tuberculous process. The second form of pseudoleukæmia, as

stated above, differs both clinically and pathologicaly from the first form. The disease runs practically a non-febrile course and the characteristic lesions are those of a lymphosarcoma. The etiology of this form of pseudoleukæmia is at present unknown. To say that the disease is essentially a multiple sarcoma throws no light upon the problem and only adds further complications.

While, therefore, recent researches have not made definite the etiology of pseudoleukæmia, the advances gained thereby have laid the foundation for a subsequent more accurate understanding of the disease. The old idea that leukæmia and pseudoleukæmia are closely related diseases is fast losing ground and should be regarded as obsolete.

It is extremely probable that under what we now call pseudoleukæmia two or more distinct diseases are included. Indeed, of this conception there can scarce be a doubt.

PATHOLOGICAL ANATOMY.—In accordance with the above subdivisions, the pathological lesions of pseudoleukæmia are twofold, according to the type of the disease present. These are, first, tuberculous lesions; and second, sarcomatous lesions. In many cases these lesions are distinct and well defined, but in others they occur in combinations of various grades. It is not necessary to enter into a detailed description of the various histological changes thus observed, as such are well known. The lesions are especially observed in the lymph glands, spleen, and liver.

SYMPTOMATOLOGY.—The symptomatology of pseudoleukæmia has been exhaustively considered in Vol. VII. of this work. It only remains to emphasize the division of the disease into the two above-mentioned clinical types. The recurrent febrile form was first accurately described by Ebstein, and by some has been designated by his name (Ebstein's disease). It is characterized by febrile and afebrile periods, which are from six to twelve days in duration and succeed each other with more or less regularity. General lymphatic glandular enlargement is usually present, but often is not a prominent symptom and is frequently not observed until the disease is somewhat advanced. The spleen is always enlarged. The urine may contain a trace of albumin and hyaline or granular casts. General symptoms of toxæmia, as headache, muscular pains, vomiting, diarrhœa, anorexia, insomnia, delirium, etc., are frequently present. In certain instances this form of pseudoleukæmia in its initial stages closely resembles typhoid fever, so that a differential diagnosis is a matter of considerable difficulty. The non-febrile form of the disease is more or less characteristic. A general enlargement of the lymphatic glands together with the spleen is early observed. Cachectic appearances and an impairment of the general system gradually supervene.

The duration of pseudoleukæmia is subject to great variation. In general it is from a few weeks (six) to two or three years. The febrile form usually runs the more acute course.

The Blood.—The changes in the blood are diversified. In some cases the blood, except for a reduction in the amount of hæmoglobin, is practically normal throughout the disease. In such cases the hæmoglobin is rarely reduced below sixty per cent. A hyperleucocytosis is rarely observed, and when present is usually of a very slight grade. A hypoleucocytosis, on the other hand, is quite frequently met with, especially in febrile cases. The erythrocytes may be reduced in number, but rarely descend below 3,000,000. Eosinophiles, especially in the febrile form, are generally increased relatively in number, as are also the large mononuclear leucocytes. Myelocytes in small percentage (three per cent.) have been reported as occasional. As can be seen by the above, the blood in pseudoleukæmia, so far as we at present know, possesses no definite characteristics.

DIAGNOSIS.—The diagnosis of pseudoleukæmia rests upon a combined consideration of the clinical symptoms and the microscopical blood appearances—that is, a general glandular and splenic enlargement with an absence of characteristic blood leukæmic changes. The greatest difficulty is experienced in the early differentiation of some of the febrile cases from typhoid fever. In such the total hypoleucocytosis is very often nearly identical. In febrile pseudoleukæmia, however, there is usually a relative increase in the number of eosinophiles, which is never the case in typhoid fever. Furthermore, the presence or absence of a Widal reaction *in a high dilution* and the successful or unsuccessful isolation of the bacillus typhosus from the fæces render the diagnosis clear.

PROGNOSIS.—The prognosis of pseudoleukæmia of either form is fatal.

TREATMENT.—The treatment of pseudoleukæmia is symptomatic and does not call for further consideration, no advances having been made since 1897. In those cases in which the lymphatic glandular enlargement is limited to a few lymphatic glands, excision of such has been recommended and practised. It cannot be shown, however, that material benefit has been gained thereby in those cases in which the diagnosis of pseudoleukæmia was valid.

Anæmia.

Anæmia may be defined as a reduction in the amount of blood as a whole or of certain of its more important morphological or chemical constituents. Anæmia may be local or general. Local anæmia may affect any of the various body tissues or organs, and is to be regarded

as a special pathological condition of such. It will not be here considered. General anæmia may be either primary or secondary. Primary anæmia may be divided into (1) progressive pernicious anæmia and (2) chlorosis.

Progressive Pernicious Anæmia.

ETIOLOGY.—Much speculation has been indulged in with respect to the etiology of progressive pernicious anæmia and many widely divergent views appertaining thereto have been advanced. Much of this chaos has resulted from a lack of accurate discrimination between primary progressive anæmia and severe or fatal secondary anæmia. It is true that such a differentiation on either clinical or pathological grounds is often extremely difficult, nevertheless it is certain that the time has come when by a proper consideration of all the factors it is possible to simplify and definitely crystallize our views concerning progressive pernicious anæmia. Hunter more than all others has contributed to this result. He regards this disease as of a chronic infective nature, caused by a definite infection of certain portions of the mucosa of the alimentary tract, usually of the stomach, but occasionally of the mouth or intestines. Clinically it is characterized by a definite series of phenomena, and pathologically by specific alterations in the blood. The definite bacterial basis has not as yet been determined. It is possible that this may be either single or multiple; that is, that the disease may be produced by only one species of microorganisms, or that in accordance with the susceptibility of the individual it may arise from the infection of any one of several species. Those who dispute this conception of progressive pernicious anæmia claim that clinically and pathologically it is impossible to differentiate between a severe or fatal anæmia arising from no detectable cause and one brought about by certain influences, such as pregnancy, intestinal parasites (bothriocephalus anæmia), etc. In certain cases this is undoubtedly true, but in such, if a comprehensive view of anæmia is taken, it is much more logical to regard these causes as apparent rather than real; for if this is not done, such cases should be classified as secondary instead of primary anæmias and the line of demarcation between primary and secondary anæmia would be lost, while recent observations have shown that in the vast majority of cases it can be definitely established.

It is unquestionably true that various predisposing causes are operative in the origin of progressive pernicious anæmia, but to suppose that such are the actual primary causes is as irrational as it would be to consider that certain nervous influences, cold, bad sanitation, etc., are the essential causes of typhoid fever, diphtheria, pneumonia, smallpox, etc.

PATHOLOGICAL ANATOMY.—The pathological lesions *in toto* have been exhaustively considered in the original edition of this work; it only remains to emphasize certain of the more important. The color of the blood as it flows from the finger prick is usually good, at least in the early days of the disease. This is due to the relative high percentage of hæmoglobin present. The color index is higher than in any other form of anæmia. Eichhorst's corpuscles are frequently present, but are not pathognomonic of the disease. They are about the size of a normal erythrocyte, are of a deep red color, and do not have a biconcave form. The leucocytes are as a rule absolutely reduced in number, but show a relative increase of the large and small mononuclears. There may, however, be a slight hyperleucocytosis. The red blood cells are always markedly reduced in number. The average number present is usually 1,000,000, but they are frequently reduced to from 200,000 to 400,000. The characteristic feature of the blood is the abundant presence of megaloblasts. These may be present in enormous or moderate relative number. Normoblasts are infrequent as a rule, and their presence may with difficulty be demonstrated. Occasionally they are fairly abundant, but their number is always exceeded by that of the megaloblasts. The size of the red blood cells is increased and many megalocytes are present. Many oval erythrocytes are also seen.

It may be considered definitely settled that the increased destruction of the erythrocytes takes place in the liver.

SYMPTOMATOLOGY.—In progressive pernicious anæmia as here considered four sets of symptoms are found in combination, and such a combination is to be regarded as characteristic of the disease. These are: (1) General weakness with extreme anæmia and the usual resultant symptoms. (2) Hæmolytic symptoms—urobilinuria and a yellow color of the skin. (3) Oral (stomatitis, etc.) and gastro-intestinal symptoms. (4) Toxic symptoms—irregular pyrexia, tingling and numbness of fingers, etc.

Any of these sets of symptoms may usher in the attack. Very often gastro-intestinal symptoms are the first manifestations of the disease.

A detailed description of these symptoms is not necessary. The important point is their combination.

DIAGNOSIS.—The diagnosis of progressive pernicious anæmia is to be made by an examination of the blood. The essential diagnostic feature is the presence of a large number of megaloblasts and the fact that these always exceed in number the normoblasts present. In no case should a *positive* diagnosis of progressive pernicious anæmia be made unless this relation between megaloblasts and normoblasts is present. In certain cases, however, this characteristic is not sufficiently

well marked to justify a positive opinion with respect to the nature of the disease. In such cases the combination of the above clinical symptoms together with the presence of over thirty-three per cent. megalocytes (Ewing) and a high color index may be regarded as sufficient for a *probable* diagnosis. A *probable* diagnosis of progressive pernicious anæmia should never be made upon a reduction in the number of the erythrocytes, no matter how marked this may be.

PROGNOSIS.—While the prognosis of progressive pernicious anæmia is extremely grave, recent methods of treatment have demonstrated that it is by no means necessarily fatal.

Great care should be exercised in making predictions upon the result of blood examinations, as observation has shown that the condition of the blood is subject to marked variation.

TREATMENT.—The treatment of progressive pernicious anæmia may be divided into specific and symptomatic.

Specific Treatment.—In accordance with his conception of the disease, Hunter has treated it with combined intestinal antisepsis and inoculations of antistreptococcus serum. His results have been eminently successful. As an intestinal antiseptic he used mercuric chloride in the daily ordinary dose. Five cubic centimetres of antistreptococcus serum were inoculated two or three times weekly for a considerable period. Since it has not been shown that the disease is due to streptococcus infection, the use of an antistreptococcus serum must be regarded as largely visionary in nature, and in our present knowledge it should be expected that the proportion of recoveries following its use would be small. In view of Hunter's results increased observations along this line are greatly to be desired.

The use of intestinal antiseptics has been recommended by various authors. Betanaphthol has been regarded by many as of especial use.

Under the head of specific treatment should be included those measures directed to a cleansing of the gastro-intestinal tract. In this manner noxious products, toxins, and microorganisms are removed therefrom. Perütz has recently drawn attention to this mode of treatment and to the favorable results to be obtained thereby. He advises that the stomach be washed out every morning with a decinormal saline solution. At night a high enema of one quart of chamomile infusion should be administered.

It is of course to be understood that any method of specific treatment must be combined with suitable dietetic and hygienic measures.

Symptomatic Treatment.—In the symptomatic treatment of progressive pernicious anæmia arsenic and phosphorus are the drugs which have given the best results. If these drugs are used they should be pushed to their physiological limits. Injections of cacodylate of sodium have been used in a few cases with good results. Iron is useless and

generally harmful. Those who have had the most experience in the use of the various preparations of bone marrow have been disappointed in the results obtained thereby. Transfusion is of no avail. The various symptoms as they arise should be met by appropriate medication. Especial mention should be made of the efficiency of suprarenal extract in the treatment of the hemorrhages so common throughout the disease.

Chlorosis.

Since 1897 but little has been added to our knowledge with respect to the etiology, symptomatology, or treatment of chlorosis. The characteristic alteration in the blood is a marked reduction in the amount of hæmoglobin and consequently a low color index. The number of erythrocytes is sligthly reduced, but rarely is less than 3,000,000. In the most severe cases normoblasts are sometimes seen in small numbers. Megaloblasts are never present. These characteristics serve readily pathologically to differentiate this disease from progressive pernicious and secondary anæmia. Clinically, however, the diagnosis of chlorosis must rest upon a combination of the blood appearances and the objective symptoms. From a prognostic standpoint an enumeration of the red blood cells is of advantage. Those cases in which this number is less than 3,500,000 as a rule respond very poorly to treatment and require prolonged observation, as they are especially inclined to relapses. Those in which this number is above 4,000,000 are as a rule readily cured.

Secondary Anæmia.

But little is to be added in this place to the consideration of secondary anæmia. The diagnosis rests upon the blood condition and hinges upon the relation of the megaloblasts to the normoblasts. In secondary anæmia the normoblasts constantly exceed the megaloblasts in number. Megaloblasts are frequently absent and are usually rare. Any anæmia should be considered secondary so long as this condition is present. Certain secondary anæmias eventually pass into the progressive pernicious form, and when this takes place the megaloblasts increase in number and exceed the normoblasts. The color index in secondary anæmia is higher than in chlorosis, but lower than in the progressive pernicious variety. The treatment of secondary anæmia is twofold: (1) The treatment of the cause. (2) Symptomatic treatment. The latter includes the use of iron, arsenic, bone marrow, and the various systemic tonics, together with proper dietetic and hygienic measures.

DISEASES OF CHILDREN.

BY

JULES COMBY,

PARIS.

Rachitis.

THERE are certain affections of the bony system which simulate rachitis, and which from the point of view of differential diagnosis deserve special attention. I refer to osteomalacia, osteopsathyrosis, achondroplasia, and cleidocranial dysostosis.

1. *Osteomalacia.*—This affection bears a singular resemblance to rachitis in the situation of its lesions, the decalcification of the bones, the softening of the skeleton, and the resulting impotence. It is, however, rare in infancy, being a disease of adult age and of the female sex in especial. Rehn, of Frankfort-on-the-Main, has described osteomalacia of infancy. We doubt the occurrence of this osteomalacia as we do that of the newly born (Stanski) or fetal osteomalacia, believing that it has been confounded with rachitis. In both osteomalacia and rachitis the bones are soft and decalcified as if they had been soaked in acid; the Haversian canals are dilated and surrounded with a myxomatous tissue composed of large anastomosed and star-shaped cells separating the thinned and irregular bony layers; owing to the presence of osteoblasts, the bone has the appearance of fetal bone at the time of absorption.

The ostalgia is intense and increased by pressure, walking, and fatigue, and is soon accompanied by muscular indolence, impotence, deformations, and curvatures which diminish the stature. At the same time the skull becomes thicker, the face appears to enlarge, and the forehead may develop knobs and depressions. The vertebral column becomes deviated so as to produce kyphosis, lordosis, or scoliosis. The ribs, sternum, and clavicles become curved and shortened. The long bones of the limbs, which are bent and atrophied, break at the slightest shock or strain, the fractures healing with the greatest difficulty or ending in pseudarthrosis. Sometimes the bones are so soft that they are not able to break, and bend in every possible way.

Osteomalacia follows a progressive course, with possible remission of varying length; the patient falls into marasmus and succumbs to some intercurrent infection. When this disease does appear in adolescents it is localized and benign (scoliosis, genu valgum, etc.), without tendency to rapid generalization.

Osteopsathyrosis.—Among the rare diseases of bones which have been confounded with rachitis is a special fragility of bone, described as *idiopathic osteopsathyrosis* (F. Schultze, *Archiv für klinische Chirurgie*, 1894; Moreau, Thèse de Paris, 1896).

The child affected by this disease is subject to fractures which are either spontaneous or the result of the slightest strain. Schultze saw a girl of thirteeen years, who had had thirty fractures of the bones of the arms and legs. She was pale and thin (an eight-months child), and began to have fractures of the bones at the age of nine months. At that age there was a fracture of the right femur. The bones were all small, the lower limbs bent, the tibiæ flattened, the feet flat, and the muscles atrophied. Osteotomies performed to remedy these troubles permitted observations as to the absence or atrophy of the medullary cavities. In the left leg the tibia and fibula were welded together by a flat exostosis occupying the interosseous space. The fractures of the upper limbs were not accompanied by pain, but those of the lower limbs were painful.

We see that this disease does not resemble osteomalacia (no softening of the bones) nor rachitis (no bending), fragility being the only point in common.

Treatment should consist of cod-liver oil, sea baths, and phosphorus (glycero-phosphates, lime, ovo-lecithin), with the purpose of strengthening the bony system.

Achondroplasia.—This affection has been and still is confounded with rachitis. As early as 1856 and 1858 Virchow had described fœtuses and new-born infants with enlarged heads and small extremities, which were classed as cases of *fetal or congenital rachitis.* In 1860 H. Müller, while retaining the latter name, showed that intra-uterine rachitis should be distinguished from the acquired. Winckler (1871) proposed the name of *Rachitis micromelica* to emphasize this distinction. Depaul (1877–1878) also recognized the necessity for such a distinction. At this juncture Parrot (Société d'Anthropologie, 1878) suggested the name of *achondroplasia.* In 1886 he gave a good description of this disease, which has since that time been distinctly differentiated. In 1889 Kirchberg and Marchand described it under the name of *Micromelia chondromalacia.* In 1889–1890 (*Nouvelles Archives d'Obstétrique et de Gynécologie*) Porak published an excellent article on the subject. In 1892 Kaufmann studied and gave a description of thirteen fetal skeletons affected with achondroplasia, and under

Chondrodystrophia fœtalis distinguished three varieties, viz., *malacica*, *hypoplastica*, *hyperplastica*. In 1893 Thompson reported three cases, to which must be added the cases of Lugeol (Société de Médecine et Chirurgie de Bordeaux, 1892), of Apert (Société Anatomique, 1895), of Herrgoth (Société d'Obstétrique, gynécologie et pediatrique, 1900), of P. Marie (*La Presse médicale*, July 16th, 1900). In this strange disease there are two salient characteristics: the enormous head and the extremely low stature, or dwarfism. The latter is due to the remarkable shortness of the legs, the trunk being normal.

Micromelia is an essential feature of achondroplasia, the victims of this disease being micromelic dwarfs. The four limbs are affected in the same way. The arm is shorter than the forearm (reversal of normal conditions), the difference being about 4 cm. The thigh is shorter than the leg. The trunk is normal and the contrast between it and the shortened extremities gives a grotesque appearance. Parrot and Porak have compared it to that of a dachshund.

Court dwarfs were probably achondroplasiacs, for they were apt to be very intelligent.

The macrocephalia is also an essential characteristic, and may even simulate hydrocephalus. The head is round, with frontal and parietal prominences; the face is large, the features are thick, the root of the nose is flat, the tip of the nose is large and rounded, the nostrils are flaring; the nose is short and thick; the palatal arch is frequently ogival.

Lumbar lordosis is very marked, the sacrum being thrown up and back, although the back is flat. In women there is contraction of the pelvis. Obesity is frequent, and the weight is great relatively to the size of the body. The hand is small in every dimension; it is square and muscular. The fingers are short and of equal length, and spreading at the extremities (trident hand). The fourth finger is on a plane posterior to that of the middle and the little finger. The lower limbs are frequently curved inwardly, because of an angular displacement of the two segments of the limb. The upper limbs are not curved. The muscles are developed to an extraordinary degree, so that the patients are veritable athletes (pygmies). The genital organs are well developed.

How are we to explain this strange affection, which is seen more often by the accoucheur than by physicians in general, the infants often dying in utero or living but a short time after birth? There is evidently some defect in the development of the bony framework at the very beginning of its formation. There is a dystrophy of the primordial cartilage accompanying the first osteogenetic activity at the third to the sixth month. Ossification by means of the epiphyseal cartilages is arrested, and the bones are unable to lengthen, while they grow in thickness by means of the periosteum. Such bones as develop

at the expense of the primitive embryonal tissue (clavicle, ribs, frontal and parietal bones), without passing through a cartilaginous stage, escape the dystrophy. This explains the remarkable contrast between the development of the trunk and that of the limbs. The radiograph shows that the epiphyses are enlarged and appear crushed, as do the cartilaginous heads above them (chondrodystrophia hyperplastica). The diaphyses have no marked incurvations. Union of the epiphyses is delayed.

Achondroplasia must be clearly distinguished from rachitis; it occurs in intra-uterine life, rachitis later; it causes no deformation of the sternum, ribs, or clavicle, does not markedly bend the diaphyses, etc.

Achondroplasiacs are usually born before term and nearly always die, although they have sometimes grown to later childhood and to adult age. Porak reports an hereditary case; March 20th, 1883, he performed cephalotripsy and embryotomy on a primipara of twenty-seven years. This woman, who was intelligent and non-rachitic, was only 1 metre 15 cm. (3 ft. 9 in.) tall. Her trunk and head were those of an adult, the nose was flattened, the limbs were short, with lumbar lordosis. Having become pregnant a second time, she was subjected to Cæsarean section on January 26th, 1887. A living child was extracted, which resembled its mother in the diminished size of the limbs, and which was an achondroplasiac.

Cleidocranial Dysostosis.—Marie and Sainton (Société médicale des Hôpitaux de Paris, May, 1897 and 1898) presented patients affected with malformations of the bones which have sometimes been confounded with rachitis. It is an hereditary dysostosis characterized by exaggeration of the transverse diameter of the cranium, retarded ossification of the fontanels, and aplasia of the clavicles. There are on record thirty-one well-authenticated cases of this singular affection.

The dysostosis is usually bilateral, but the clavicular aplasia rarely goes so far as total absence. Either a parasternal or a paracromial vestige usually persists. The parasternal rudiment, generally bony, and regular or swollen at its extremities, or conical, articulates with the sternum, the other extremity being free. There may be two rudiments, the sternal and acromial. There may be a small or a large space between them, or the ends may overlap. During rest one is struck by the fact that the shoulder appears to be sunken and thrown forward, and by the absence of the clavicle. The acromion projects beyond the head of the humerus, and there is a subacromial cavity or notch into which the finger can be inserted, as in cases of dislocation of the shoulder. There are no supra- or subclavicular fossæ, the thorax being directly continuous with the neck. Spontaneous motion of the limb and muscular force are normal, but there are additional

abnormal movements which give bizarre attitudes—forced adduction of the shoulders, with possible contact of the heads of the humerus, or the posterior borders of the scapulæ may touch each other or even overlap. As the clavicle is absent, the arm can of course take the most surprising positions. In addition to the clavicular dysostosis, there are dysostosis of the cranium, depression between the frontal prominences, sinking of the anterior fontanel, and projecting forehead, with the frontal bosses very salient. The projection of the parietal bosses is the more striking as the face, which is small, is retreating in relation to the frontal plane. The median suture which separates the frontal eminences is prolonged between the parietal bones (natiform cranium). The projection of the parietal bones enlarges the transverse diameter of the cranial vault. The temporal plates are slightly developed, the occiput is flattened. The fontanels may persist until adult age, being open in one case in a woman of forty-seven years. There may be Wormian bones, in the sagittal and lambdoid sutures. The base of the skull is shortened, perhaps curved in an arch with the convexity upward corresponding to the spheno-occipital synostosis.

The face is atrophied, the nose deformed, the bones of the nose being reduced about one-half, the inferior border of the orbit retreating in relation to the superior, the transverse diameter of the inferior maxilla diminished. The palatal arch is decidedly ogival; the teeth are of tardy development, defective, badly implanted. So that, as far as the cervico-facial skeleton is concerned, there is defect, arrest, or deviation of the normal ossification.

Yet the patients are intelligent, without hydrocephalus or hypertrophy of the brain. The head is apparently enormous, but the volume of the skull is normal. The disease is familial and hereditary, but is not transmitted beyond the second generation. Moreover, in the same family not all the children are affected. Those who escape the dysostosis frequently have other deformities (clubfoot, etc.). What is the cause of the disease? Scheuthauer holds that there is early intra-uterine inflammation (first or second month); Dowse speaks of congenital atrophy; Schorstein of intra-uterine rachitis. These are merely hypotheses.

It is a curious thing that cleidocranial dysostosis attacks the very bones which achondroplasia does not affect. These two dystrophies appear to supplement each other. Perhaps the cause should be sought for in syphilis, tuberculosis, alcoholism, intoxications, and infectious diseases contemporary with procreation and gestation. The pathogenesis of the disease is wrapped in obscurity.

Diseases of the Digestive Tract.

Macroglossia.—In this disease the tongue is too large, fills the mouth, and projects from it. The condition is usually congenital. There is no true hypertrophy, but lesion of the parts: sclerosis, interstitial glossitis, lymphangioma, erectile tumor (elephantiasis). The epithelium is thickened, the papillæ are voluminous and filled with leucocytes, the submucous tissue is in partitions, the muscular fibres are dissociated, thinned, and choked by the connective tissue or the blood-vessels.

The child's mouth is partly opened, it drools, and nurses with difficulty. The tongue protrudes, and is dried and irritated by contact with the air; it becomes hard, dry, black, rough, and cracked. When teeth appear they press upon, ulcerate, and cut the tongue. The inferior incisors are pushed outward, deviated, and become loose. Mastication, deglutition, and speech are interfered with. Sometimes the child cannot take either breast or bottle and has to be fed with a spoon. A spontaneous cure may occur in a few months, so that the physician should not be in haste to intervene (de Molènes, Société médicale de Chirurgie, May 9th, 1898). The various methods of treatment resorted to are compression, ignipuncture, ligature of the lingual arteries, and amputation.

Ranula.—Ranula is a salivary cyst of the floor of the mouth. It may be sublingual or suprahyoidean. In the first case its seat is in the sublingual glands; it is lateral, ovoid, parallel to the inferior maxilla. The second variety is found in the submaxillary glands, and projects externally below the chin. These tumors are soft and fluctuating and contain a clear fluid. They are troublesome only because of their size, as there is no inflammation. Incision does not suffice, but the sac should be excised internally through the buccal mucosa.

Angina Ludovici.—This affection is a phlegmon of the floor of the mouth—inflammation of the serous sac of Fleischmann, found chiefly in adults, but occurring also in children, and sometimes even in the newly born (three cases in Cocar's Thesis, Paris, 1895). The frænum of the tongue is pushed upward by a hot and painful inflammation, the tongue is pushed back, the gingivolingual groove is replaced by a hard and painful swelling. Suction, deglutition, and phonation are interfered with. The tumor may be unilateral or median. With the progress of the disease the suprahyoid region becomes swollen and painful. At the same time the general systemic condition is bad, there are fever, anorexia, and a generally alarming condition. An incision should be made through the mouth as soon as pus has collected, and boric-acid washings given.

Inflammation of the Submaxillary Glands.—In addition to submaxillary mumps, there is a submaxillitis which may occur as a primary affection in newly born infants (Chassante-Baroz, Thèse de Paris, December 21st, 1899), or may be secondary (typhoid fever, etc.). It consists in an infection of the salivary gland, starting from the mouth and making its way through Wharton's duct. A small tumor, the size and shape of an almond, may be felt on one or both sides under the maxilla. External pressure on the tumor will cause an exudation of pus through the opening of Wharton's duct, under the tongue. The tumor increases in size, pushes up the floor of the mouth, pushes back the tongue, and interferes with nursing. An examination of the pus has shown the presence of streptococci and staphylococci.

In some cases there are fever, emaciation, and rapid athrepsia; in others the child, which is already cachectic, does not react and quietly dies. In the diagnosis we must first eliminate Ludwig's angina, ranula, mumps, and submaxillary phlegmon. Prognosis is grave, because of the extreme youth and weakness of the patients. Prophylaxis consists in keeping the mouths of nursing infants very clean and in not allowing the child to nurse a diseased breast (galactophoritis). An effort must be made to empty the gland by expression before nursing, and if an abscess forms it should be incised.

Periodic Vomiting.—Periodic or cyclic vomiting in late childhood has been described by Whitney (*Archives of Pediatrics*, 1898), then by Rachford, Crozer Griffith, Comby, Solelis, Valagressa, and Marfan (*Archives de Médecine des Enfants*, 1901). Its characteristics are the following: A child of healthy appearance, who is perfectly well in the intervals of the crises, every two or three months or perhaps every six months has attacks of incoercible vomiting which last for several days, accompanied or not by fever, but usually by constipation. The breath has a decided odor of acetone. The attack ends as suddenly as it began. The children affected are usually of the neuroarthritic type, whose parents are gouty, asthmatic, nervous, or subject to migraine, etc. After a series of crises the disease ends in recovery, but it is impossible to say when this will occur. It is an arthritic manifestation (Comby: "Arthritism in Childhood," *Archives de Médecine des Enfants*, January and February, 1902). Treatment consists in abstinence from food and injections of artificial serum; later of a vegetable diet.

Stenosis of the Pylorus.—According to the observations of Meltzer (*Medical Record*, August 20th, 1898), Ed. Cantley (*British Medical Journal*, November, 1898), Still (Pathological Society of London, February 17th, 1899), Pfaundler (*Wiener klinische Wochenschrift*, 1898), and others, there exists in some newly born infants a hypertrophic stenosis of the pylorus which is usually congenital. Some see in this

merely a spasm of the sphincter of the pylorus; others consider it an hypertrophy of the muscular fibres. In any case the result is an almost insuperable obstacle to the passage of food, and unless intervention be speedy the child will succumb.

The symptoms are the following: incoercible vomiting from the first days after birth, no bile in the vomited matters, and obstinate constipation; the abdomen is not distended, or only in the epigastric region. By palpation we may sometimes feel a small tumor in the region of the pylorus. Recovery is rare, the children usually dying with the symptoms of inanition and athrepsia. In the case of some children who had sufficient resisting powers, early intervention (pylorectomy) has resulted in cure. In other cases in which the stenosis was slight, recovery followed the use of medicinal means.

Malignant Disease of the Stomach has been met with in about ten patients under fifteen years of age. Dr. James Finlayson (*British Medical Journal*, December 2d, 1899) saw a boy of three and a half years die rapidly of primary sarcoma of the stomach. Th. Williamson (*London and Edinburgh Monthly Journal*, 1841), Cullingworth (*British Medical Journal*, 1877), Kuhn (*The Lancet*, 1897) have reported cases in the newly born, and Widerhofer saw a case in a nursing infant of two months (*Jahrbuch für Kinderheilkunde*, vol. ii.), which would seem to prove that gastric sarcoma may be congenital.

Among older children we find the cases of Ashby and Wright (eight years), Moore (girl of thirteen years), Scheffer (boy of fourteen years), Jackson (boy of fifteen years). An instructive study of this subject has been published by W. Osler and McCrae (*New York Medical Journal*, April 11th, 1900).

The tumors, which are sometimes sarcomatous, sometimes encephaloid or epithelial, are situated either at or near the pylorus, or near the cardiac end. They are often latent to the very end, and the diagnosis, which is almost impossible, is indicated only by the appearance of glairy or bloody vomit, or by the cachexia. Palpation may reveal a tumor in the epigastrium, but the greater possibility of a tumor of the peritoneal cavity, of the kidney, or of the spleen averts suspicion from the stomach.

Progress is rapid and the prognosis is grave. Were it possible to establish an early diagnosis, gastroenterostomy might be attempted; and if the tumor were limited to the pylorus it might be possible to save the patient's life.

Digestion Fever.—This is a fever which appears a little while after eating, and is connected with the processes of digestion (Charrin, *Journal de Chimie*, 1889). The digestive juices are sometimes pyretogenous, and the fever which they cause takes on an intermittent character coinciding with digestion. The children attacked are nearly

all chronic dyspeptics, badly fed or overfed, great eaters and drinkers, etc.

The child, pale, thin, without appetite, in the evening after eating has a more or less severe fever with hot skin, perspiration, restlessness, disturbed sleep. The attacks return every day at the same hour, or at longer or shorter intervals. The affection is not of long duration, but is very liable to return. Malaria is to be taken into account, but this disease is not affected by quinine. Tuberculosis occurs to the mind, but the close connection of the fever with digestion causes the pendulum to swing in the direction of digestive autointoxication.

A well-regulated diet, intestinal antisepsis, laxatives, and life in the open air cause a disappearance of the attacks.

Acute Intestinal Septicæmia of Later Childhood.—Under this title I have described (*Médecine moderne*, November, 1896) a choleriform disease which attacks children, not in early infancy, but between four and ten years of age; dyspepsia, overeating, overdrinking, the effect of heat have all been considered causes of the affection; there is no contagion nor are there epidemics. There is autointoxication, due to the coli bacillus. The onset comes with indigestion; colic, vomiting, frequent but not abundant stools. There is irregular fever. The stomach is absolutely intolerant of food. The child falls into an algid state, the urine is suppressed, and death occurs within two or three days. Prognosis is very grave, yet some children have recovered.

Water diet, iced and gaseous drinks, lavage of the stomach and intestines, hot baths, energetic rubbings, injections of artificial serum, of ether, caffeine, sparteine, or camphorated oil are indicated.

Tuberculosis of the Digestive Tract.—In children, as in adults, tuberculosis of the digestive tract is nearly always due to the swallowing of tuberculous sputum, *i.e.*, it is generally secondary to pulmonary tuberculosis. The possibility of intestinal tuberculosis due to ingestion of the milk or the flesh of a tuberculous animal is to be taken into account, but it is practically of little importance.

Buccopharyngeal Tuberculosis.—The tongue and the pharynx may be attacked. Tuberculosis of the tonsils, adenoid vegetations, and granulations of the pharynx are well known. A little girl of four and a half years (Isambert, Société médicale des Hôpitaux, 1876) had an ulceration of the velum palati and the pillars of the fauces, with granulations that looked like semolina or like fish eggs.

Tuberculosis of the Stomach.—The usual lesions are ulcers and granulations. The patient may suffer from hæmatemesis, vomiting, diarrhœa, and sometimes melæna and peritonitis. In thirty tuberculous children, whose ages ranged from four months to two years, I found tuberculous ulcerations of the stomach three times.

Intestinal Tuberculosis.—This situation is three times more usual

than the preceding (eight times in thirty tuberculous children). The small intestine is usually the seat of the affection, especially the ileum, Peyer's patches, and the follicles; it is also seen in the cæcum, where it causes a species of hypertrophic tuberculous typhlitis, in the appendix, and in the colon. There are granulations and more or less deep ulcerations. All these lesions are caused by the swallowing of pulmonary sputa, or by the migration of bacilli through the blood-vessels. The symptoms consist of chronic diarrhœa, melæna, progressive cachexia, sweating, hectic fever, anasarca, etc.

Tuberculosis of the Mesenteric Ganglia.—This lesion, known as tabes mesenterica and mesenteric phthisis, is closely connected with intestinal tuberculosis. The mesenteric ganglia become more or less voluminous masses, round, mobile, and indurated. On section we find tubercles in various stages (infiltration, caseation, suppuration). Sometimes large mesenteric tuberculous abscesses are formed. Caseation of the mesenteric ganglia is always preceded by intestinal tuberculosis. The peritoneum around the ganglia is not usually affected, so that tuberculous peritonitis is not the necessary consequence of intestinal or ganglional tuberculosis; the two localizations are entirely distinct and not interdependent.

Mesenteric phthisis, however, is a very grave affection, which indicates a profound and generalized invasion of the organism by tuberculosis. Recovery is rare, difficult, and greatly delayed at best.

Sarcoma of the Intestine.—Malignant tumors of the intestine are not rare in childhood, and Dr. Ablon (Thèse de Paris, June 23d, 1898) was able to collect a dozen cases. The tumor is usually situated in the second portion of the small intestine, the ileum, or the jejunum, but is sometimes met with in the duodenum. It forms a circular prominence above which the intestine is dilated in ampulla form. The walls of this canal are much thickened and of cancerous aspect. The mesenteric ganglia are invaded. Sometimes the omentum, the liver, kidneys, etc., are the seat of secondary cancerous foci. Under the microscope we find small round cells with large nuclei. It is in the submucous layer that intestinal sarcoma originates. It may be congenital.

The symptoms are the following: Continuous or paroxysmal abdominal pains, occurring spontaneously or after eating; abdomen much enlarged, while the rest of the body becomes emaciated or œdematous (œdema of the legs). No ascites. Palpation reveals a tumor in the side, in the iliac fossa, below the umbilicus, etc. The growth is hard, irregular, sometimes lobular, and mobile. It may, however, be smooth, regular, and a trifle soft. Small at first, it is of rapid growth, and may sometimes be felt through the rectum. There is constipation at first, or else constipation alternating with diarrhœa; later there are frequent liquid, fetid stools, with blood, pus, and mu-

cous débris as in dysentery. There may be vomiting of food or bile. Icterus, pleurisy, and pulmonary congestion have all been noted. There are generalized adenopathy, profound anæmia with emaciation, and progressive marasmus. The disease is of rapid course, going through its whole development in a few weeks or two or three months at most, and is inevitably fatal.

The diagnosis lies between tumors of the omentum, mesentery, kidney, ovary, tabes mesenterica, etc. Treatment is of little value. Should the diagnosis have been made sufficiently early and the general condition be good, removal of the tumor may be attempted.

Intestinal Lithiasis.—In the stools of children suffering from enteritis, especially of the mucomembranous variety, we frequently find sand. This lithiasis, which I have found from the age of eighteen months to that of fifteen years, is of arthritic origin. The parents have gout, obesity, asthma, etc. The intestinal sand is brown or reddish in color, and, according to Berlioz, has the following composition:

Fatty matters		8.50 per cent.
Other organic matters		45.22 "
Mineral salts 51.28	Phosphoric acid	23.32 "
	Lime	26.85 "

The symptoms are crises of pain, colic with or without vomiting, followed by the expulsion of mucomembranous, glairy matter, mixed with sometimes enormous quantities of sand. The pain is usually limited to the iliac fossæ and to the course of the colon. Diagnosis is reached by examination and sifting of the fecal matters. Treatment consists of alkalies, draughts of water, baths, and a vegetable diet.

Stercoral Tumor, or Stercoroma.—In excessively constipated children we may find tumors in the abdomen formed of accumulated and indurated fæces.

A rachitic child in my clinic had a hard and mobile tumor which one of my pupils supposed to be sarcoma of the intestine. But the indolence and the shape of the growth made me recognize it as a stercoroma, and large lavages of the intestines caused its disappearance.

A boy of fifteen years (Dubourg, Société de Médecine et Chirurgie de Bordeaux, May 20th, 1898) had a mobile, subumbilical tumor. Laparotomy was performed, the descending colon was incised, and a fecal mass weighing 720 gm. was removed.

Congenital Dilatation of the Colon.—Examples of this affection have been reported by Hirschsprung (*Jahrbuch für Kinderheilkunde*, 1888), Mya (1894), Treves (*The Lancet*, January 29th, 1898), Concetti (Meeting of German Naturalists and Physicians, Munich, 1899), etc.

The trouble consists of a considerable dilatation of the large intes-

tine, with hypertrophy of the muscular fibres, without contraction as a rule, although in some cases there is congenital stenosis of the large intestine. Symptoms are obstinate and permanent constipation which necessitates constant enemata, ballooning of the abdomen, vomiting, hiccough, and dyspnœa from pressure on the diaphragm. The child gradually becomes emaciated and falls into marasmus. Death occurs from intestinal obstruction or from enteritis. Some cases, however, of a less serious nature may recover under suitable diet, electricity, and intestinal irrigation. Resection of the intestines, performed with good results by Fr. Treves, is applicable in desperate cases.

Bacteriology of Enteritis.—Since the day that Escherich discovered the bacterium coli in the stools of a nursing infant, an important rôle has been attributed to this microbe in the gastroenteric affections of childhood. Lesage (1887) describes it as the microbe of green diarrhœa. W. Booker (1887–97), in addition to the *bacterium coli* and the *lactis aërogenes*, found the *proteus vulgaris*, and the *streptococcus*. He classifies (1) Dyspeptic diarrhœa, with the *B. coli* and as an accessory the *B. lactis;* (2) gastroenteritis due to the *proteus* manifested by a choleriform intoxication without extensive lesions; (3) gastroenteritis with *streptococci*, producing intestinal ulcers and general infection.

Escherich divides the intestinal infections into exogenous and the endogenous. Baginsky does not believe in an exogenous origin, but holds that the *coli*, *lactis*, *proteus*, and *pyocyanic* are all normal residents of the intestines, capable of being stimulated into virulency by heat and errors of diet. A. Czerny believes that the bacteriology is overshadowed by overfeeding and acid intoxication (excess of ammonia in the urine). In truth there are no specific microbes in infantile diarrhœas.

Bacterium coli and allied species. An examination of the stools, cultures, and serum reaction do not demonstrate the specificity of these bacilli. When the B. coli penetrates into the blood during life, it is because of its virulency (colibacillary bacteriæmia causing bronchopneumonia, meningitis, etc.). Whether the coli bacillus can come from without, through the milk and the food, is a question still under debate.

Streptococcus. According to Escherich and his school, there is a streptococcal enteritis (streptococcus brevis, S. gracilis). This is the form observed in follicular or mucomembranous enteritis resembling the enterococcus of Thiercelin. It is more usual in the autumn and winter than in the summer.

Staphylococcus pyogenes. This microbe is supposed to be derived from the milk of inflamed breasts (abscess, galactophoritis, etc.). Karlinski found the staphylococcus in the milk of the mother and in the intestines of the child.

Pyocyanic bacillus. This microbe is also supposed to be of external origin, imparts a bluish-green tint to the stools, causes hyperpyrexia, hemorrhagic eruptions, and a rapidly fatal septicæmia. It can be found in the blood (Czerny).

Proteus vulgaris. W. Booker has often found this microbe in cases of summer diarrhœa with grave general intoxication.

Proteolytic bacteria. These microbes (bacillus subtilis, B. mesentericus vulgatus, tyrothrix tenuis) pollute the milk at the moment of nursing, and are found in the stools of bottle-fed infants.

Bacillus enteritidis sporogenes. This microbe was isolated by Klein during an epidemic.

[*Bacillus dysenteriæ.*—The Shiga bacillus was found by Duval and Bassett in over forty cases of summer diarrhœa of infants (*Medical Record*, September 13th, 1802.)]

Yeast. The saccharomyces ruber has been found by Demme in milk and in the stools of nurslings who had used the milk.

Protozoa. The monoceramonas and the amœba coli are, according to Epstein, the cause of certain diarrhœas.

Associated microbes. Several varieties of microbes may be associated, especially in chronic diarrhœa. But the bacteriology of enteritis in childhood is far from settled.

Diseases of the Liver.

Congestion.—Congestion of the liver is a common affection in childhood, and is often dependent on digestive troubles, gastric or intestinal autointoxications. In addition to these commonplace causes there are intoxications (alcohol), toxi-infections (eruptive fevers, diphtheria, malaria, typhoid, tuberculosis, etc.), and icterus shown by acute and active congestion. Passive congestion is observed in cardiac affections, and in lung diseases which weaken the heart. The liver is large and soft, intensely red in color, sometimes black and hemorrhagic; on section there is much oozing of blood. In the passive congestion of cardiopaths we find the *nutmeg liver;* on section, we find the suprahepatic vein dilated, black, and surrounded by a dark red zone which is of a gray pallor at the periphery. Under the microscope we see dilatation of the central and peripheral veins, dilated capillaries, fatty degeneration of the hepatic cells, and proliferation of embryonal cells; the dilated vascular network flattens the liver cells and causes their atrophy. The organ is increased in size, indolent, smooth; there is no jaundice. The urine is scanty, dense and dark colored, containing urobilin and reddish-brown pigment. There are sometimes symptoms of gastric disorder, anorexia, tympanites, alternation of constipation and diarrhœa; in grave cases there are epistaxis, purpura, and œdema of the legs. The hepatic congestion of infectious

diseases is not conspicuous, and it is only by palpating the borders of the liver that we can estimate its increase in size.

Treatment will depend on the etiology. If there are dyspepsia and gastroenteritis, we should secure intestinal antisepsis by means of divided doses of calomel, a milk diet, and purgatives. If there is jaundice we must give the alkalies. In cases of asystole, digitalis must be administered; in malaria, quinine.

In cases of acute congestion we may apply cold compresses locally, and try the effect of large rectal irrigations of cold water to stimulate the cholagogue function. These acute congestions in children are but transitory, and soon disappear.

Fatty Degeneration of the Liver.—This affection is the result of grave infectious diseases, whether acute or chronic: variola, scarlatina, diphtheria, typhoid, syphilis, tuberculosis, etc. It is also seen in gastroenteritis, rachitis, and poisoning (arsenic, phosphorus, alcohol).

The liver is large, soft, and yellowish throughout its whole extent or in spots (marbled). The microscope shows a fatty infiltration disseminated in the lobules, fat droplets filling the hepatic cells and the vascular endothelium. The fat soon replaces all the cells.

The symptoms differ very little from those due to hepatic congestion. The liver is large and smooth, and not painful. But the child is thin, of an earthy pallor, and cachectic. A study of the causes will confirm the diagnosis. Prognosis is grave, yet recovery is possible, for there is fatty infiltration rather than true degeneration. All fats must be excluded from the diet, especially cod-liver oil. Milk and water are to be given, baths and skin rubbing administered. No alcoholic drinks should be allowed.

Amyloid Degeneration of the Liver.—This condition is observed especially in the course of chronic suppurations—cold tuberculous abscess, chronic osteitis, tuberculosis. It is also met with in syphilis, rachitis, malaria, and leukæmia. The organ is enlarged, lardaceous, and waxy. A section of amyloid liver treated with the tincture of iodine becomes mahogany colored, and then blue if treated with sulphuric acid. The amyloid substance is deposited in the middle coat of the capillaries, which become thickened. The spleen, kidneys, and heart are invaded as well as the liver.

The liver may become gigantic without having its functions impaired. The urine is normal; the spleen enlarged.

The intestines become affected, and a yellow and fetid diarrhœa results. At the termination of the disease there may be albuminuria. Pallor, œdema, marasmus, and multiple hemorrhages complete the picture. An effort must be made to prevent amyloid degeneration of the liver by treatment of the chronic suppurative processes, treating the syphilis by mercury, etc.

Diseases of the Umbilicus.

In the newly born infant the umbilicus is very vulnerable to disease.

Omphalitis.—If the umbilical wound have defective cicatrization, and be soiled by the dressings and infected, the region will become of a bright-red color, and feel hot and indurated. There will be a central suppurating ulcer. There may be a true phlegmon or a subcutaneous abscess. In other cases there is umbilical erysipelas, or gangrene which may be complicated by hemorrhage, peritonitis, or intestinal perforation (artificial anus). In addition to umbilical lymphangitis, which is found in simple omphalitis, and umbilical erysipelas, there are obliterative arteritis (Runge) and umbilical phlebitis, in which the cord is filled with pus which extends from the umbilicus to the liver. In the latter case septicæmia and death usually follow a period of fever, agitation, and coma. All this occurs within the first fortnight of life. Prophylaxis consists in properly dressing the cord after its section performed aseptically at birth.

Umbilical Fungus.—This consists of an ulceration and a subacute benign inflammation. The umbilicus, instead of healing, suppurates for a week or two. A granulation, which becomes purulent and is sessile or pedunculated, is seen within it. It should be cauterized with silver nitrate and dressed with some absorbent and antiseptic powder.

Umbilical Adenoma.—In this case there is a diverticulum of intestine with its glands and goblet epithelium. It must be excised and the pedicle cauterized with the thermocautery.

Omphalorrhagia.—If the cord have been too loosely tied there may be hemorrhage; this must be guarded against. After spontaneous detachment of the cord, grave hemorrhage may occur in the case of children suffering from syphilis, hæmophilia, etc. The umbilicus must be pinched, tied in mass, and the hemorrhage stopped at any cost.

Respiratory Organs.

Stridor of the Newly Born.—The affection known as stridulous respiration of the new-born infant is at last beginning to be understood. A sound like the croaking of a frog, a sort of gurgling noise, is heard during respiration, without there being the slightest spasmodic effort, dyspnœa, cyanosis, or any sign of asphyxia. It is increased by screaming and excitement, lessened during sleep, and disappears spontaneously after having lasted months or years. Of eighteen children observed by Sutherland and Lambert Lack (*Lancet*, September 11th,

1897) eight had attacks of suffocation on awakening. Auscultation of the lungs gives negative results; so usually does examination of the larynx. Still, in six cases a laryngoscopic examination showed the epiglottis to be folded over on itself, its margins being almost in contact; the arytenoepiglottic folds were so near each other as to reduce the size of the laryngeal opening and impede respiration, while their flapping made it noisy. The vocal cords were clear. According to Gee, the noise originates in the pharynx; Lori holds that there is spasm of the vocal cords, Robertson that there is paralysis of the dilators of the glottis, Thomson a defective innervation, Herzfeld a disturbance of the respiratory centre.

It is, however, probable that, in conformity with the opinion of Lees, Goodhart, Sutherland, Variot (Société médicale des Hôpitaux, May 27th, 1898), the trouble is due to a congenital malformation of the larynx with flaccidity of the arytenoepiglottic folds. With growth the folds become firmer and less floating and the stridor disappears. In a recent article (*Archives de Médecine des Enfants*, December, 1901) Dr. L. Cerf divides congenital stridor into several varieties: (1) Vestibulary wheezing; (2) snoring from adenoids; (3) wheezing from tracheobronchial adenopathy; (4) wheezing from hypertrophy of the thymus; (5) wheezing from obstetrical laryngitis; (6) wheezing of nervous origin. The disease is benign and recovery ultimately ensues without treatment.

Diseases of the Thymus Gland.

This transitional organ, situated in front of the mediastinum and in intimate relation to the trachea which it separates from the sternum, may present various lesions.

Absence.—In a child of two years affected with myxœdema, I found absence of both thymus and thyroid glands; to this absence of the thymus I attributed the early appearance and the severity of the disease. The child was scarcely larger or heavier than a new-born infant. When the thymus is well developed it seems able to take the place of the thyroid body, and it is perhaps for this reason that the manifestations of an absent thyroid are delayed in nurslings.

Hypertrophy.—Hypertrophy of the thymus is of frequent occurrence in the newly born and in nursing infants; very often we may find a thymus gland weighing 15, 20, 25, 30 gm. and more. It is evident that a gland of this size, being unable to develop anteriorly because of the sternum, might compress the trachea and so cause sudden death. Cases of this nature have been reported in children of two months (Clessin), of seven months (Koppe), of ten months (Biedert), etc.

Phlegmasia.—Inflammation of the thymus is rare. Still Demme

saw a boy two and a half months old who had an inflammatory swelling in the front of the neck, with dysphagia, dyspnœa, cyanosis, tachycardia, and fever. At the autopsy an abscess of the thymus was found. Paul Dubois had previously seen suppuration of the thymus in syphilitic fœtuses; soft gummata and syphilitic cysts of the thymus have been reported by Depaul, Lehmann, and Bednar.

Tuberculosis.—I have found caseous masses in the thymus of a child who had at the same time bronchial adenopathy. In a little girl forty-two days old, Demme discovered three tubercles of the size of a hazelnut, with Koch's bacilli, in the thymus. Hence this gland can evidently be invaded by tuberculosis.

Various Tumors.—Neoplasms (sarcoma, myxoma) have been noted in the thymus. Stendener saw a round-celled hemorrhagic sarcoma in the thymus of a year-old child. The symptoms given were those of a tumor of the mediastinum.

Peripheral Polyadenopathy.

In addition to the ordinary scrofulotuberculous adenopathies there are, even in early childhood, generalized ganglionic affections which are described under the name of polyadenopathy or micropolyadenopathy. Are these tuberculous? The researches which have been made sometimes result positively and sometimes negatively; there are evidently virulent (bacillary) lesions and non-virulent ones (scrofulous).

Etiology. External tuberculous adenopathies are observed at all ages. I have seen them in infants at the breast. They are found in delicate lymphatic patients, the victims often of heredity.

Sometimes, however, the patients are robust and vigorous. The immediate cause escapes us—how did the bacillus penetrate into the ganglion? If a child is attacked by tracheobronchial adenopathy, one naturally supposes that it has been infected through the bronchi; tabes mesenterica suggests intestinal infections. If then we find the subcutaneous ganglia becoming tuberculous, we should examine the skin or the adjacent mucous membranes for the point of entrance; this point may sometimes be observed (eczema, otitis, coryza, amygdalitis, blepharoconjunctivitis), but often it is absent or overlooked. In some cases the infection of the ganglia takes place through the blood-vessels, and cervical scrofulous glands may be the direct result of inhalation. The bronchial ganglion is first affected, and then the cervical. In short, we must take into account any contagious process and any lesions of the neighborhood which may have preceded the adenopathy. Cornet (Eighteenth Congress of the German Surgical Society, 1889) placed tuberculous sputum on the ocular, nasal, and buccal

mucous membranes of dogs, and obtained caseation of the cervical ganglia without any macroscopic lesions of the neighboring mucosa.

The ganglia appear as hard masses of a light yellow or grayish color on section, some may be larger, and are soft, yellowish, and evidently caseous; a creamy or puriform liquid flows on section. Others are stony in texture, chalky, or filled with a plaster-like substance. Sometimes suppuration invades the ganglia and the surrounding cellular tissue, and large or small cold abscesses follow the adenopathies.

Sanchez Toledo (Thèse de Paris, 1887) studied tuberculous adenopathy of the axilla, and showed its relation to pleuropulmonary tuberculosis; this adenopathy may be isolated, or may follow tracheobronchial, subclavicular, or even cervical adenopathy. In any case it may be propagated to the pleura and to the lungs by means of the intercostal ganglia and lymphatics.

The onset is insidious. Occasionally there is only one ganglionic mass which develops either at the angle of the jaw, or beneath the chin, or in a subclavicular or axillary depression; sometimes numerous ganglia project on either side of the neck (polyadenitis). The tumors are hard and roll away from the finger. Sometimes in the neck there are enormous hardened masses which simulate lymphadenoma (this is the hypertrophic form of ganglionic tuberculosis). But if the disease progress, softening soon follows induration; the ganglion is large, soft, and painful; the overlying skin is adherent to its surface and becomes purple; fluctuation appears and the tuberculous abscess is formed. These abscesses either open spontaneously or have to be opened by the surgeon; in the latter case the sequelæ may be quite simple, and a cure without unpleasant cicatrization may ensue. In the former case a veritable livid ulcer is formed, in the depths of which are granulations or caseous matter that is eliminated very slowly. The cicatrices are irregular, projecting, and defacing; sometimes they give rise to keloids which may be indolent or painful.

To sum up—slowness of development, torpor in the symptoms, a very feeble tendency toward repair, and permanent cicatrices are the principal characteristics of tuberculous adenopathy. It must not be forgotten that the development of this disease may be interrupted and shortened by a visceral tuberculosis which has arisen from it.

Given a swelling of the glands, we must make sure of its origin. A skin lesion (eczema, impetigo) or a mucous lesion (coryza, angina) might occasion a simple adenitis. In case of doubt a bacterial examination can be made, or the inoculation of tuberculin tried.

As to the micropolyadenopathy of Legroux, it does not always indicate latent tuberculosis, although Hutinel, Marinescu, Lesage, and Pascal have found the Koch bacillus in a few cases. Potier has met with this polyadenia in cachectic, non-tuberculous children.

The physician should be extremely conservative, and unless there be some special indication, as suppuration, he should not operate on cases of chronic adenitis. Hygienic and medical treatment, open air, sea air, and proper feeding will do more good than the knife, although perhaps more slowly.

Diseases of the Heart.

Paroxysmal Tachycardia.—There is in childhood a cardiac neurosis which is exhibited in painful and serious attacks of palpitation; this is essential paroxysmal tachycardia (Bouveret). The disease is more rare in children than in adults; it is seen chiefly in later childhood, five, ten, or twelve years of age. The personal history of adults sometimes shows that the attacks have been in existence from the earliest years. Girls are more often affected by this disorder than boys. Essential tachycardia occurs chiefly in families with a nervous or neuro-arthritic history.

This affection is probably a pure neurosis, without primary cardiac lesion. Yet at the time of the attack, and sometimes in the intervals, the heart is large and dilated, and one is led to suspect pericardial adhesions, degeneration of the myocardium, etc. According to Henningham the heart is not normal, it being affected either by acute rheumatic or syphilitic myocarditis, or by a neuritis. But this is purely hypothesis.

Symptoms. At intervals of weeks or months, there are attacks consisting of violent palpitations with a sensation of agony and oppression. The pulse beat is 150, 180, 200, 220, 240, and it is small and weak; the face is pale, the respiration accelerated. There may be a strong heart beat coexisting with the feeble pulse. Examination of the precordial region shows a marked increase in the area of dulness; it was doubled in the case of a girl of thirteen years observed by Merklen (Société médicale des Hôpitaux, May 10th, 1901). The lung may be congested (bloody sputa), and so may the liver. A species of sudden, temporary asystole is produced by acute dilatation of the heart. The urine, which is diminished in amount during the disease, becomes abundant afterward (polyuria). There may be some fever.

The crisis appears and terminates abruptly. From one day to the next the pulse falls from 200 or 220 to 100, 90, 80. The cardiac impulse becomes quieter, the area of dulness normal. The duration of the disease varies in different cases, and attacks may vary in the same case. Prognosis is serious, but not grave, for these attacks of tachycardia rarely end in death. The disease is a very painful neurosis, with frequent relapses, and of indefinite duration, which, according to some may become complicated by lesions of the myocardium.

Diagnosis. Recognition of the condition is not difficult; we merely have to count the pulsations. If the attack is not a first one, there will be a history of previous paroxysms, of their length and their frequency. This will suffice for the diagnosis of paroxysmal tachycardia; there remains the elimination of lesions of the endocardium, the myocardium, and the pericardium. A study of the personal and family history of the patient with regard to constitutional or hereditary taint will complete the diagnosis.

Absolute rest in bed is demanded, with mental and physical calm. Light diet—milk, bouillon, light drinks. To relieve the cardiac distress we may try opium, potassium, or ammonium bromide, and the valerianate of zinc or of ammonium. Subcutaneous injections of morphine hydrochlorate are indicated in very painful cases complicated by suffocation. Merklen had brilliant success from the application of four leeches to the precordial region. The actual cautery and blisters may also be applied.

Arrhythmia.—When the heart beats are of unusual strength and duration, and are interrupted by real or apparent intermittences, there is said to be arrhythmia. The term may apply to the number or to the force of the beats (unstable or unequal pulse). If a pulsation is suddenly lacking ("false step" of the heart, claudication) we say that the pulse is intermittent. Tachycardia and arrhythmia are not associated, since irregularities cannot be appreciated in a very rapid pulse, but bradycardia is often found with arrhythmia. In the acute and febrile stage of tuberculous meningitis, as in the same period of other acute diseases, arrhythmia is not present, but it is shown when the fever falls and the pulse becomes slowed.

The causes of cardiac arrhythmia are very numerous. In addition to organic affections of the heart which in the asystolic stage nearly always cause arrhythmia, and in addition to cerebral affections, tuberculous meningitis especially, of which arrhythmia is one of the usual symptoms, we may classify the other causes in six principal groups:

1. The arrhythmia of healthy children. Children of any age and in excellent health may have an irregular pulse. I have noticed it in nursing infants as well as in older children, during sleeping and waking hours, but especially during sleep. There are intermissions, "false steps," or a series of rapid followed by a series of slower pulsations. This arrhythmia is not constant—it occurs spontaneously or after over-exercise, fatigue, bicycling, etc. It may be the result of mental excitement, and is more frequent in nervous children than in others. It is of no pathological importance, and may be regarded as essential or physiological arrhythmia.

2. Toxic arrhythmia. Poisoning by the Solanaceæ (belladonna, hyoscyamus, stramonium), by opium, digitalis, ether, chloroform, or

carbon dioxide, in fact any accidental or therapeutic intoxication may cause this condition.

3. Arrhythmia of gastrointestinal origin. All affections of the digestive tract, from simple indigestion to the most marked infection, may by a veritable autointoxication interfere with the rhythm of the heart. Dyspeptic, constipated children with dilatation are very often troubled with arrhythmia, and if at the same time they have headache, one is apt to fear meningitis. Catarrhal jaundice and intestinal worms often cause the symptom.

4. The arrhythmia of dyscrasia. Arthritism (obesity, diabetes, asthma, migraine, etc.), anæmia, chlorosis, rachitis, intermittent albuminuria, and too rapid growth may all cause arrhythmia.

5. Neurotic arrhythmia. An irregular heart is frequent in Sydenham's chorea (cardiac chorea), and is seen also in hysteria, epilepsy, the cerebral excitement of young persons, masturbation, etc.

6. Arrhythmia of convalescence. In convalescence from acute febrile diseases there is often a slowing of the pulse with irregularities, "false step," and more or less marked arrhythmia. If in such cases the irregularity and slowness of the pulse are accompanied by pallor, nausea, and faintness, we should be on the lookout for myocarditis.

In convalescence from febrile diseases of long duration, the arrhythmia might be attributed to weakness, inanition, and anæmia. But when the cardiac rhythm is observed to change after short febrile processes, influenza, and abortive pneumonia just as frequently as after prolonged fevers, this explanation is not satisfactory, and one is led to believe that the regulating centres of the heart's action are affected by the toxins and the microbes in the circulation. Sometimes the arrhythmia is purely nervous, or it has its source in intoxication. In either case the blood carries with it poisons which affect not only the endocardium but the nerves and ganglia of the heart, the medulla, and the nuclei of the pneumogastric. Section of the latter nerve causes acceleration of the heart beat; its stimulation causes slowing, and the brothers Weber have demonstrated that the vagus is the moderating and the inhibitory nerve of the heart.

If a child has a slow, weak irregular pulse, should alarm be felt? If it is a case of accidental or of therapeutic poisoning arrhythmia indicates saturation, and suppression of the remedy will check the symptom. If it occur during convalescence from an acute disease, it is a critical arrhythmia of good augury, indicating the approach of recovery. Anxiety should be felt if it is accompanied by pallor and extreme weakness, with nausea and algidity, for the heart may stop beating, bulbar paralysis being imminent.

Before deciding that arrhythmia is symptomatic of meningitis, we must take into consideration all causes capable of producing slowness

or irregularity of the pulse, and will as a rule be able to exclude so alarming a diagnosis.

Essential, neurotic, emotional arrhythmia calls for no special treatment. Physical and mental hygienic precautions are to be taken—life in the open air, hydrotherapy, the suppression of all exciting conditions. In cases of accidental or therapeutic poisoning the cause must be counteracted. If digestive autointoxication be suspected intestinal antisepsis should be applied by means of purgatives, calomel, or benzonaphthol. Intestinal worms are to be expelled by the anthelmintics usually given. The critical arrhythmia of convalescents furnishes no indications for treatment, unless accompanied by collapse and algidity. In that case, frictions, stimulants, injections of artificial serum, ether, caffeine, sparteine, or camphorated oil, inhalations of oxygen, mustard baths, electricity, etc., are to be tried.

Asystole.—Asystole is to the heart what uræmia is to the kidneys—it betrays insufficiency of the cardiac muscle, whose weakened contractions are unequal to the task of sending the blood through the arterial system with the necessary force. Pressure is too weak in the arteries, too strong in the veins. This results in stasis in all the organs, in serous transudations into the subcutaneous tissues, in the cavities and in the parenchyma. The circulation being poor, the functions of lungs, kidneys, liver, stomach, intestine, and brain are interfered with. We soon have all the symptoms of asystole and cardiac cachexia. The latter is more rare in children than in adults, but it is met with not infrequently, for its causes are numerous.

The exhaustion of the contractile power of the myocardium and the heart failure which results, may be due to an old rheumatic endocarditis which for a long time has been compensated for by the youth of the muscle, the suppleness of the arteries, the absence of atheroma and of alcoholic taint. The trouble, however, finally gains the victory over the motive power, especially if a fresh inflammatory attack occurs, and if there is pericarditis or cardiac symphysis.

Besides this classic form there is acute asystole, which sometimes occurs in acute infectious diseases, rapidly poisoning and altering the muscle and nerve tissues of the heart by toxins. Acute asystole may also occur in rheumatism when there is endopericarditis, with early symphysis, compressing the myocardium as in a vice. The parenchyma and coverings of the heart are all affected; this rheumatic carditis is not uncommon in childhood.

In addition to acquired diseases, there are congenital malformations and affections producing cyanosis or "blue sickness." Cold, fatigue, mental emotion, or bronchitis suddenly increasing the work demanded of an unstable heart, may determine an attack of asystole.

If a child has heart disease, the possibility of asystole should be

foreseen, and everything possible should be done to avoid it. The patient must be warmly dressed, covered with flannel, protected from cold and dampness which might induce bronchitis and weaken the heart. He should spend the winter months in the South. Cold baths and douches are to be avoided, but cutaneous stimulation, dry or aromatic friction, massage, passive movements, Swedish movements, mechanotherapy, by facilitating the circulation and stimulating the nerves without fatigue and without making the patient breathless, can scarcely fail to be useful.

Physical and mental fatigue and excitement are to be avoided. The heart must be saved all shock, but the child must not be condemned to seclusion, nor be deprived of air and exercise. Heavy and indigestible food must be forbidden, the child being fed with milk, eggs, cream, purées of meat and vegetables, fish and stewed fruit. No wines nor cordials. The meals should be light and regular.

If there are indications of recent inflammation, of relapses, of cardiac erethism (fever, rapid heart beat, palpitation), revulsive treatment should be applied by means of the actual cautery, flying blisters, or the ice bladder. Simple palpitation can be checked by the bromide of potassium or sodium. Thin, cachectic children should be given cod-liver oil. Iron is not to be prescribed, for it is not easily assimilated, irritates the stomach, and causes congestion of the cardiopulmonary apparatus. Hæmoglobin, arsenic, and potassium iodide may be given.

With the first symptoms of asystole attention should be given to the emunctories, those safety valves of the system. Diuretics and purgatives should be administered. German brandy should be given in combination with syrupus rhamni (1 gm. for each year); if the mixture is rejected, it can be replaced by an injection of the sulphate of sodium and senna, 1 gm. for each year, and 250 gm. of water. In children who are cyanosed and suffering from suffocation, bleeding may be useful. Inhalations of oxygen can be tried. Digitalis may be given combined with squills and scammony, or with calomel. Digitalis should be prescribed for only four or five days. In urgent cases injections of caffeine should be given (10 cgm. for each year, divided into two or three doses), or of the sulphate of sparteine, 4 to 5 cgm. a day. Lactose may be added to the milk in the proportion of 40 to 50 gm. per litre, to favor diuresis. Convallaria, strophanthus, and theobromine may be given a trial.

Roger's Disease.—This is a congenital interventricular opening. The partition separating the left from the right ventricle may be totally or partially absent. In the latter case it is the posterior portion of the anterior septum which is lacking. The septum may be perforated in its inferior or median portion. The opening may be circular or semilunar, very rarely triangular, with a diameter of 5 to

10 mm. It is covered with smooth endocardium and admits the tip of the little finger. The lower border is never notched.

Auscultation reveals a systolic murmur which is permanent, non-variable, rasping, and heard in the median portion of the precordial region. Its maximum intensity is at the internal part of the third left intercostal space, and of the fourth rib, with no propagation to the blood-vessels. The murmur is sometimes so intense that it reaches the base and the apex and is heard in the back even at some distance. There is at the same time a marked systolic purring thrill felt at the seat of the murmur. These are practially all the symptoms. There are no functional troubles, and the patient may live a long time. There is no cyanosis.

Acquired perforations of the septum following ulcerative endocarditis or an aneurysm are irregular, notched, and vegetating. They are usually recognized only at autopsy. Roger's disease is clinically distinguished from other congenital heart diseases, especially constriction of the pulmonary artery with persistence of Botal's foramen, not only by the presence of the special systolic murmur which has been described, but by the absence of cyanosis, and by the perfect tolerance toward the lesion.

Anasarca.

Under this name is described a serous infiltration, a dropsy of the subcutaneous cellular tissue. Leaving aside the anasarca symptomatic of albuminuria and of asystole, we will describe idiopathic anasarca.

Anasarca is frequent in young children; out of 78 cases reported by Barthez and Sanné, 35 were primary and 43 secondary (scarlatina); chronic anasarca is due chiefly to tuberculosis and to enteritis. Cold has been considered a cause, and in fact the disease is observed in the winter only—more especially in December and January. Of the 78 cases of Barthez and Sanné, 49 were in boys and 29 in girls. The cases were more numerous from two to seven than from seven to fourteen years. If we admit the causative action of cold, how shall we explain its action? The vasomotors are paralyzed by the cold, the vessels lose their tone, and serum transudes into the subcutaneous connective tissue. In cachectic conditions dyscrasia and heart weakness are added to the effect of cold, so that in addition to the anasarca there are various visceral dropsies.

The skin is swollen, pale, smooth, and soft. Its folds are smoothed out, it pits on pressure, and is colder than normal (cold œdema). Distended by infiltration it becomes dry and scaly. The œdema is more marked in dependent portions, especially if the anasarca is partial and of moderate proportions. It is also more marked wherever the skin is thin and the cellular tissue loose. The round

and puffy limbs lose their shape, the articulations are partly immobilized. The swelling is especially marked on the dorsal surface of the hands and feet. Arterial pulsations are deadened, and it is only by fairly crushing the œdema that we can take the pulse.

According to the course of the disease we distinguish the following varieties: 1. Acute primary anasarca which is sometimes ushered in by fever, is limited to certain regions or is general, is isolated or accompanied by visceral dropsies. 2. Chronic secondary anasarca accompanying pulmonary tuberculosis and cachexias in general, lasting weeks or months with remissions and exacerbations. The urine may be scanty or abundant and contains no albumin. Acute anasarca usually has a favorable termination; out of 63 cases studied from the point of view of prognosis, Barthez and Sanné noted 49 cures and 14 deaths. In the acute form the complications, such as internal dropsies, phlegmasia, and convulsions, are what cause death; in the chronic forms tuberculosis as a rule brings about the fatal issue.

We can easily distinguish anasarca from subcutaneous emphysema, effusion of blood, and sclerema neonatorum. By examination of the urine we can tell whether the anasarca is idiopathic or due to Bright's disease; an examination of the heart will decide as to asystole. The disease once recognized, we must ascertain whether the cause is cold, or previous acute disease, as scarlatina, measles, etc. In cases of persistent œdema tuberculosis is to be suspected.

The child must be kept warm, wrapped in cotton batting, put in a room at 20° or 22° C., given hot drinks, friction with hot flannels, massage; hot air and vapor baths have been given with success. For collapse, brandy, digitalis, coffee, injections of sparteine, of artificial serum, etc., must be tried.

The Urinary Organs.

Hydronephrosis.—Should any obstacle to the flow of urine exist at any point of the urinary tract the fluid collects above it, and dilating the ureter and the pelvis of the kidney constitutes hydronephrosis.

The obstruction may be situated in the pelvis, ureter, bladder, or urethra. The tumor may be congenital, resulting from malformation or contraction of the ureter, from its vicious insertion into the bladder, from imperforate urethra, or from phimosis. It may be acquired, the result of the presence of a foreign body (calculus or parasite) in the urinary passages; or of flexion (movable kidney) or of external pressure (tumor of the kidney, pelvic tumor, etc.).

The acquired hydronephrosis of nursing infants usually originates in renal lithiasis; during the course of several autopsies I found a brownish urate-like powder at the normally constricted portions of

one or the other ureter, which by its accumulation prevented the passage of urine. My interne, M. L. Bernard, has published an article on this subject ("Sur l'Hydronéphrose Calculeuse," *Archives de Médecine des Enfants*, June 1st, 1898).

Hydronephrosis may be single or double, partial or total, unilocular or multilocular, destroying the renal parenchyma or leaving it normal. In severe cases the pouch of fluid pushes the renal tissue upward and outward, atrophies and destroys it. While smooth and polished on its inner surface, it may be divided into cells by many septa (multilocular nephrosis). Incision of the pouch gives issue to a fluid which is usually clear, but which may be thickened, dark, and reddish. If the trouble is of recent date, as when due to obstruction by a calculus or a tumor, the fluid is like urine. The hydronephrosis may be purely ureteral, as in a case which I observed in a little girl of six months; an abscess of the pelvis having compressed the neck of the bladder, the latter was distended and the two ureters were equally dilated, but the pelves of the kidneys were not altered. In some cases of renal lithiasis the hydronephrosis may be confined to the ureter by an accumulation of sand and gravel at some point in the lower part of the canal. The ureter then is fusiform or cylindrical, as large as the intestine, without there being any distention of the kidney pelvis. It is very probable that in such a case the passage of the urine is only partially arrested.

In cases of long standing the fluid loses its urine-like character and becomes serous, seromucous, albuminous, charged with epithelial cells, blood corpuscles, leucocytes. The specific gravity is lessened (1.007, 1.010), urea and the phosphates are diminished.

The kidney is atrophied, hard, sclerosed, sometimes entirely destroyed and replaced by a fibrous membrane. The size of the tumor varies from that of an egg to that of a child's head. If the obstruction is situated high up, the hydronephrosis is limited to the kidney pelvis; if very low, near the meatus, all the urinary passages are involved and death is inevitable.

The hydronephrosis may be latent, and in all the cases which I have seen in nursing infants the disease was found only at autopsy. There is an indolent tumor which must be sought for and palpated with the greatest care. The flank is obliterated, bulging, pushed upward by a fluctuating tumor, dull on percussion, not painful on palpation. Should the tumor be very large, it may cause trouble by that fact alone, induce dyspnœa by pressure on the diaphragm, or cause constipation by impeding the progress of the fæcal matters; there is no fever. The urine is normal except in the case of intermittent hydronephrosis with its alternate swelling and subsidence, its urinary "breakings up" as it were. At such times the urine is

clear, lessened in density, hyponitrogenous. Such intermittences are seen in movable kidney, flexions, and twisting of the ureter; they may also be met with in cases of lithiasis. The course is slow and torpid, and the prognosis varies according to the cause. Congenital hydronephrosis is incurable with rare exceptions; the double is more grave than the single. Hydronephrosis due to calculi or compression, and intermittent hydronephrosis may be cured, but there is always danger of anuria and uræmia.

Diagnosis is difficult. If the hydronephrosis is of small extent it does not attract attention; when large it does not escape notice, but it may be mistaken for ascites, ovarian cyst, cyst of the liver, kidney or peritoneum, for sarcoma, etc. In ascites we have the extent of the swelling and its symmetry, fluctuation, the shifting of the fluid with change of position, the collateral circulation, etc. Cyst of the mesentery is median in position and mobile in every direction. Ovarian cyst is at first developed in the hypogastric region, and forms a round tumor which projects anteriorly. By puncture we obtain a clearer and thinner fluid. Other kidney tumors are less soft, more easily felt, of more rapid growth, and more threatening in their effect on the general condition. Pyonephritis might be confounded with hydronephrosis, but it will not escape notice that the urine is not clear and leaves a deposit of pus.

The hydronephrosis once recognized, it must be ascertained whether it be due to calculus, movable kidney, compression, or congenital stenosis. The history of the case, taken in conjunction with a local examination, will usually suffice to complete the diagnosis.

Treatment will vary according to the cause. Where there is displacement of the kidney, nephrorrhaphy is indicated to prevent flexion of the ureter. If the ureter is defectively inserted, surgical intervention may be called for. Outside of these cases treatment is for the most part merely palliative, and consists of repeated punctures. Extirpation was done with success in a case of Schattauer's (*Centralblatt für Chirurgie*, 1887); there was immense hydronephrosis of the left side, of several years' standing, in a child of seven years; 11 litres of fluid were drawn off by puncture. After retroperitoneal extirpation recovery ensued in five weeks. John Thomas Shirlaw performed nephrotomy with success on a boy nine weeks old who had a left congenital hydronephrosis (*British Medical Journal*, November 16th, 1901).

Tuberculosis of the Kidney.—Tuberculosis of the kidney occurs in two forms, discrete miliary tuberculosis (medical tuberculosis) and caseation *en masse* (surgical tuberculosis). Miliary tubercles of the kidney are secondary and occur with frequency in generalized miliary tuberculosis. In 28 autopsies on tuberculous children, I found renal

granulation four times, or 1 in 7. The liver and spleen are more often the seat of miliary tuberculosis. Of the 28 cases quoted above, these organs had tubercles in 13 cases. I must add that in this series all the children were nursing infants. The renal tuberculosis was discovered only at the autopsy.

On the other hand there are certain cases in which the tuberculosis appears to develop primarily in the kidney, where it reaches a considerable degree of severity; the organ is increased in size, covered with protuberances, filled with caseous cavities; the pelvis and the calices are dilated and distended by a puriform fluid (pyonephrosis). The caseation is propagated to the ureter and bladder, and soon the whole urinary excretory apparatus is invaded by tuberculosis. At the autopsy we usually find a unilateral tuberculosis which has transformed the kidney into a cavernous sac filled with chalky matters; the kidney substance proper is no longer in existence, the walls of the pelves and ureters are thickened, these organs being dilated, ulcerated, unrecognizable. Sometimes the ureter is constricted or obliterated. Abscesses from associated microbes may form in the kidney or in its neighborhood (tuberculous perinephritis). Frequently section of the diseased kidney will show rather distinctly limited cystic cavities containing a caseous fluid; these cavities may be entirely closed or may be intercommunicating. This caseous degeneration of the kidney is seen only in later childhood; I have never found it in nursing infants. The onset usually escapes observation. There may be a history of slight or abundant hæmaturia at long or short intervals. Even in the primary forms renal tuberculosis may not be perceived; pain is absent, and hæmaturia is rare. But the urine is muddy and contains pus, and must be examined with care. In one case the urine was abundant and sometimes passed involuntarily, and the patient was considered to be suffering from nocturnal enuresis. He had no fever nor pain of any kind. One day he very suddenly died, and there was found complete caseation of the right kidney propagated to the ureter and the bladder. There was also recent pulmonary tuberculosis. Patients die of uræmia or of marasmus.

We can sometimes perceive on the right or the left side a knobby, hard, and painful tumor, which may be fluctuating if there is pyonephrosis. I felt such a tumor very distinctly in the case of two little girls whom I examined. To recognize its nature, the urine should be examined bacteriologically, and in doubtful cases it should be used to inoculate guinea-pigs. The disease lasts from six to eighteen months. In some cases the general condition is unaffected; in others it is profoundly altered, the children becoming thin, pale, and cachectic. This progressive hectic condition is seen especially when there is complicating tuberculous cystitis. If one kidney only is

affected (and this we may sometimes ascertain by means of the cystoscope), surgical intervention becomes possible. Nephrotomy or nephrectomy will be performed according to the indications. The former is a palliative measure allowing of disinfection and draining of an infected focus in pyonephrosis; the latter removes the source of the evil. Unfortunately it is not possible to mark out the boundaries of tuberculosis; one kidney is diseased, but its companion may be also, and the ureter and bladder are often infected. In case of abscess Morgan advises nephrotomy with drainage, with nephrectomy later. If the disease is in a less advanced stage, both kidneys should be examined, and if only one is diseased nephrectomy performed.

Tuberculosis of the Bladder.—Tuberculosis often begins in the kidney and descends through the ureter to the bladder. But in some cases it may begin in the latter organ. In any case there is extremely painful cystitis. The child desires constantly to urinate, but sometimes passes only a few drops at a time of a thickened or bloody fluid. Thick flakes, blood clots, masses of pus are found in the urine: Pyuria, hæmaturia, and pain are the symptoms of cystitis. According to Armandon (Thèse de Lyon, 1897), these symptoms are occasionally lacking, being replaced by incontinence of urine.

Vesical tuberculosis, which is more rare in the child than in the adult, may be primary or secondary. When the latter, it is due, as we have seen above, to descending bacillary renal infection. It is then of great gravity, for however successfully treated it is sure to return, reinfection being possible at any moment. When primary it may yield to appropriate treatment. When the tuberculous nature of the cystitis has been recognized by means of examination of the urine with recognition of Koch's bacillus, and the inoculation of guinea-pigs, the child must be placed under the best hygienic conditions, be given milk and cod-liver oil, and have the bladder washed out; if the pain is very sharp, suprapubic cystotomy with curetting of the ulcerations should be performed.

The Genital Organs.

Tumors of the Testicle.—The testicular tumors found in children are the tuberculous, syphilitic, cancerous, and congenital.

Tuberculosis.—Tuberculosis of the testicle and the epididymis is not rare in early childhood, or at least not more so at this age than later. I have seen tuberculous epididymitis at fourteen months. Out of 20 cases collected by Jullien in the Trousseau hospital, 6 were under one year (1 at one month, 2 at two months, 1 at three months, 1 at four months, 1 at ten months), 6 between one and two years; 8 between two and thirteen years. The left testicle is more frequently

affected than the right. It has been said that the affection is often primary—it is so in the sense that the child appears to have no other indication of tuberculosis. Where then is the point of entrance? In my opinion it is in the respiratory apparatus, testicular tuberculosis being preceded by some caseous tracheobronchial ganglion, from which dissemination occurs through the circulation.

As a rule only one testicle is affected, the left more often than the right; the body of the gland is first invaded, then the epididymis and sometimes the cord.

The onset may consist of an acute orchitis (tuberculous orchitis), with swelling, heat, and pain; the symptoms subside at the end of a few days, and the chronic process is established. As a rule the course of the disease is insidious and we discover the lesion only by palpation. Softening follows induration, and then come abscess and fistula. In many cases, however, there is no suppuration and the tumor terminates in resolution. The child may have other lesions elsewhere, including tuberculous meningitis. Spontaneous cure is not infrequent.

Treatment should be conservative; castration is not to be performed; Vigo's plaster may be used, the tumor may be protected, and proper hygienic measures should always be taken.

Syphilis.—Hutinel has demonstrated the frequency of hereditary testicular syphilis. This may be shown at birth, or developed only after a few months or after the first year. The lesion is usually bilateral, and the body of the testicle only is affected. There is no fluid in the tunica vaginalis, and the organ is hard and firm, and indolent, rolling around in the sac like a marble. Syphilitic sarcocele does not soften, but is the seat of a sclerogummatous process which nearly always ends in atrophy and sterility. The treatment is the same as in other forms of syphilis—mercurial inunctions and iodide of potassium.

Cancer.—Malignant tumors of the testicle are fairly frequent, and some time ago (*Progrès médical*, 1884), Ch. Monod was able to get together twenty-seven cases. In about half the cases the disease declares itself in the first year of life, and often in the first six months—sometimes indeed it appears to date from birth. Between the ages of one and two years cases are numerous, but they are quite exceptional after the age of three or four years. Heredity has not been distinctly traced except in one of Hutchinson's cases, in which two of the child's aunts were found to have died of cancer. Traumatism, as crushing of the testicle, has been considered responsible, but the injuries are often found to have occurred to a gland that was already diseased. The general condition is good and the tumor is painless, but it grows with rapidity. On either the right or the left side we find a tumor as large as an egg, resistant, pseudofluctuating, opaque, heavy, insensible to pressure. The surface is smooth or slightly uneven. The gland is

more affected than the epididymis. The cord is healthy, and the lumbar glands are intact. The skin is not adherent or vascular. Hæmatocele may be suspected, especially if there is a history of traumatism. But puncture gives issue to only a little blood, and the trocar is not felt to be free in a cavity. Moreover, hæmatocele does not exist in children.

Hydrocele may be distinguished by the fluctuation, transparency, and the result of puncture. Tuberculosis attacks the epididymis as well as the body of the organ, occurs in successive attacks, causes abscess and fistula, and never attains a large size. The sclerogummatous testicle of syphilis has too characteristic an appearance to be mistaken. Scrotal inclusion caused much perplexity in a case reported by Verneuil.

If the tumor is left to itself it may invade the skin and cause an ulcer; in the long run the lumbar ganglia become affected and cancerous cachexia is established.

Prognosis is very grave, in spite of castration, and a relapse occurs in six months or a year. Even in cases in which the operator found the tumor to be an enchondroma or a testicular cyst, the result was bad. In any case operation must be performed without delay. As conservative as we should be in tuberculosis, just so radical should we be in cancer of the testicle. Castration is obligatory.

Hydrocele.—An effusion of serum in the tunica vaginalis following inflammation of the testicle or the epididymis is rare in children, and does not differ from the acquired hydrocele of adults. There is a form of acquired hydrocele in the newly born, the result perhaps of chilling during labor, and developed a few days after birth. It is irreducible and perfectly translucent, and disappears spontaneously within a few weeks.

Congenital hydrocele is of different origin, and depends on the persistence of the vaginoperitoneal canal, which in the first few days of life forms a communication between the vaginal and the peritoneal cavities. Ramonède found this communication thirty-two times in two hundred and fifteen cases. There may even be strangulation in this communicating canal, producing vaginal hydrocele, encysted hydrocele of the cord, or Dupuytren's hydrocele. In the last-named variety, the scrotal sac communicates by means of an inguinal canal with the iliac sac. In these cases the fluid is clear as in all hydroceles. The testicle is either in its normal position below and behind the scrotum, or above, inverted, or not yet descended.

Inguinal hernia may exist with hydrocele. As a rule the hydrocele is found at birth, but it may be delayed, following the descent of the testicle. It occurs as a smooth, regular tumor, elastic, fluctuating and transparent, with flexible walls. There is no gurgling sound

during reduction, nor any sonorousness under percussion, which facts permit of the elimination of hernia.

The prognosis is benign, and as a rule recovery is spontaneous. Treatment may hasten recovery if it be limited to compression, and the application of resolvents (five-per-cent. ammonium chloride) or ether sprays. In obstinate cases it may be necessary to incise, or to give injections of alcohol, tincture of iodine, or zinc chloride.

Gangrene of the Scrotum.—A gangrenous inflammation of the scrotum and of the prepuce is sometimes seen in new-born infants and in nurslings, which in spite of its rarity deserves mention.

The cases reported by F. Brun and A. Broca (*Gazette hebdomadaire*, April 11th, 1900) were in children seventeen and twenty-one days old. Another child seen by Broca was two and a half years of age. After this age the affection becomes quite exceptional, to reappear in adult life, when venereal and vesical troubles play an important part in the pathogenesis. In the child there is no infiltration of urine, nor specific chancre. The infection comes through an erosion irritated by the dejecta; it may be situated on the genital organs or at the beginning of the thigh. I have seen a case caused by a burn. As a rule the children are vigorous and healthy and breast-fed; in one case of the kind I was unable to find the place of entrance of the infection.

The onset, which often escapes observation, consists of a superficial lymphangitis, with redness of the parts, fever, prostration, refusal of the breast. The scrotum and the penis are much swollen, hot, red, tense, hard, and painful, so that micturition is difficult. The skin soon acquires purple plaques, and a white, hard, and completely mortified surface is seen on the scrotum and penis. It is at once identified as gangrenous inflammation. The point of entrance of the infection is sometimes so small that it cannot be found, but it is very evident that it does exist or has existed on the skin, for the affection is clearly of external, cutaneous, streptococcal origin.

If the general condition of the child be good, prognosis need not be bad, no matter how severe the appearance of the lesions.

In some cases phimosis complicated by strangulation at the base of the gland (paraphimosis) gives inflammatory and painful symptoms which raise a doubt. But in addition to the appearance of the penis, there are not the purple and sphacelous spots seen in gangrenous phlegmon. As infiltration of urine practically does not exist in the newly born, it does not need to be taken into account.

Treatment should be prompt and radical. At the very beginning of the disease, large incisions should be made with the bistoury at the points of greatest tension, and the relaxation following will be remarkable. To avoid loss of blood, which is always of bad effect in the newly born, the thermocautery may be used to pierce the scrotum at

two or three well-chosen points. If the child's general condition is good, this measure will be followed by a prompt cure.

Phimosis.—This consists of a malformation of the prepuce preventing uncovering of the glans, and even interfering with micturition. It is an exaggeration of the normal condition, with constriction of the orifice and frequently with balanopreputial adhesions. The latter are easily detached, and after circumcision we see masses of smegma accumulated around the glans, especially at the corona. This of course opens the way to various infections, balanitis, balanoposthitis, purulent discharges, eschars. I have seen a case of true septicæmia with great rise and fall of temperature following simple phimosis. Circumcision puts an end to these troubles. If the phimosis is very constricted or if the preputial orifice and the meatus do not correspond, the flow of urine is much impeded; there may be retention, nocturnal or diurnal incontinence, masturbation, rectal prolapse, hernia, or convulsions. Calculi may be formed in the preputial sac which is distended by urine. There may be paraphimosis, the prepuce being drawn backward causing strangulation of the glans or of the prepuce itself, which becomes swollen, œdematous, ulcerated, etc.

Various forms of treatment have been suggested for phimosis. 1. Dilatation under anæsthesia, by means of hæmostatic forceps; this is applicable to certain cases. 2. Incision, which is not to be recommended. 3. Excision which is the procedure to be preferred; the skin in front of the glans is cut with scissors, and after retraction of the prepuce the mucosa in front and behind it is incised on the cannula and the adhesions are detached; circular section follows, and skin and mucous membrane are brought together by means of catgut sutures or spring forceps. The dressing should consist of a dry antiseptic powder.

Anomalies of the Genitalia in Little Girls.—Among the anomalies found by the physician are vulvar adhesions, vulvar hemorrhages, precocious menstruation, and metrorrhagia.

Vulvar Adhesions.—As imperforate hymen causes trouble only at the time of menstruation, it may be passed over in this connection. The labia may be soldered together by a membrane, or be merely slightly united by a cellular adhesion which can be torn apart by a very slight effort. As a rule the membranous flap is not entire, but has an opening at its upper portion through which the urine finds a more or less direct point of exit. When the urethral orifice is completely covered, there is retention of urine in the bladder or an accumulation of urine at the vulva. A grooved sound gently manipulated will usually suffice to break down the obstruction, but we may need to use a bistoury guided by the sound. Henoch advises detachment of the labia with the handle of the scalpel; Kirmisson uses a probe; any instrument almost will do if it has been sterilized in boiling water.

The clitoris is sometimes found to be adherent to its mucous covering; these adhesions, which are a possible source of itching and a cause of masturbation, must be broken down.

Vulvar Hemorrhages.—In addition to the vulvar hemorrhages of new-born female infants we notice in older children losses of blood which are due to an inflammatory process. The vulvo-vaginitis of little girls is frequently accompanied by hemorrhages which might easily be mistaken for metrorrhagia or for premature menstruation. I have shown that this flow of blood is allied to vulvitis (Société médicale des Hôpitaux, October 23d, 1896). The blood has its source in a fungous granulation situated at the urinary meatus, which has by several authorities been regarded as urethral prolapse. By separating the thighs of the child and endeavoring to insert a soft catheter into the urethra, we cause a hemorrhage which comes from neither vagina nor bladder, but from the meatus. Cauterization of the bleeding point with the mitigated stick or with a 1 to 50 silver-nitrate solution will stop the bleeding. In some cases there is evident prolapse, and excision must be performed (Broca).

Premature Menstruation.—When the blood comes from the vaginal canal and the uterine cavity, there is premature maturity. There have been cases of little girls menstruating at eight, six, three, and even two years. They are developed far beyond their age; they have large breasts, and the mons veneris is covered with hair.

Dr. V. Gautier (*Revue médicale de la Suisse Romande*, November 15th, 1884) made out a table of 28 cases of premature menstruation, which might be added to at the present day. Of these cases, 19 occurred in the first year and 9 in the second year. To these 28 cases during the first two years of life must be added 11 between two and six years.

There is little use in discussing this anomaly for which there is no remedy; the children who menstruate so early are abnormal, and according to Unger frequently become chlorotic; they are certainly the victims of a pathological taint.

Dysmenorrhœa and Metrorrhagia.—The menstrual troubles which occur in young girls whether normally or prematurely developed deserve mention. Puberty is not always ushered in quietly and normally. It may be accompanied by pain, by nervous affections, by modifications of the blood flow, by hemorrhages.

At first the menses are rarely absolutely periodical. They may appear once and then not for several months. Or after having been regular for five or six months they may stop for three, six, or twelve months. The child suffers from pain at the period, and becomes nervous and irritable, or pale and chlorotic.

Some young girls have more or less severe metrorrhagia. Accord-

ing to Lamy ("Des métrorrhagies chez les jeunes filles à l'époque de la puberté," Nancy, 1896), this trouble is observed in two classes of young girls, the one anæmic or chlorotic at the time of the first menstruation, and the other in good health. In the former case the loss of blood is preceded and presided over by a general debilitating cause; in the second some local lesion is to be suspected (virginal metritis, metritis of the cervix with vascular granulation, salpingo-oophoritis, the results of a previous vulvovaginitis, etc.). In cases of metrorrhagia with no apparent lesion, prolonged rest in bed must always be prescribed, and the usual hæmostatics be administered—ergotin, hamamelis, hot douches, etc. If there is anæmia, it should be overcome by iron and a suitable diet. Virginal metrorrhagia is rarely of a grave nature. In a few months the menstrual function becomes regularly established, and the trouble disappears.

Dr. A. Siredey ("Les ménorrhagies essentielles des jeunes filles," *Journal des Praticiens*, December 16th, 1899) believes that local causes are of extreme rarity, although cases have been reported of uterine myoma, hypertrophic lengthening of the cervix, metritis, salpingo-oophoritis, sclerocystic degeneration of the ovary; etc. He believes the cause to be a more general one, such as disease of the heart (especially mitral obstruction), albuminuria, chlorosis, hysteria, infectious diseases, intoxication from quinine and the salicylates, etc.

In many cases a neuroarthritic diathesis is the occasion of the trouble, which brings metrorrhagia into close connection with the epistaxis of young people. As provoking causes we have too long walks, running, bicycling, riding, and dancing. These exercises must be given up and the patient remain in bed during the whole of her period. The arthritic diathesis calls for its especial treatment.

Ovarian Cysts.—Cysts of the ovary are often congenital, whether they are manifest at birth by a considerable tumor, or whether they develop later. Some of them are dermoid, and contain fragments of bone, hair, cartilage, etc. The cyst may be parovarian, seated in the tube, the broad ligament, etc. The symptoms are nearly always the same—a tumor of regular shape, enlargement of the abdomen, distinct or slight fluctuation, dulness which does not change with a change of position of the child. On puncture we obtain a fluid which may be clear or oily, viscid and thick.

The cyst may be simple or multilocular. Vaginal examination is of course out of the question, but by combining rectal with abdominal examination we can ascertain the connections of the tumor very well, and distinguish it from cysts of the peritoneum, solid tumors of the kidney, congenital or acquired ascites, chronic tuberculous peritonitis, congestive abscesses, tuberculous mesenteric abscess, mesenteric cysts, hydatid cysts, etc.

After having ascertained the nature of the cyst by exploratory puncture, extirpation by laparotomy should be taken into consideration. This operation has often been performed, and successfully, not only in older children, but in nursing infants, several months old. D'Arcy Power reports a case of ovariotomy followed by recovery in a child of four months (*British Medical Journal*, March 5th, 1898). In another case, a child of twenty months was successfully operated on for dermoid cyst.

Nervous System.

Cerebral Congestion.—Congestion of the brain is frequent, but as a rule it is secondary to meningitis, convulsions, fevers, cardiac affections, lung diseases, etc.

The vessels of the pia mater are injected, filled with blood, the sinuses being engorged with black blood. On the surface of the convolutions we see a more or less deep uniform red color, or else purple spots of greater or less extent. On section we find a black or red mottled surface which indicates the involvement of the deep vessels of the cerebral substance.

Doubtless, these congestive lesions, whether superficial or deep, diffuse or localized, do not of themselves constitute a disease. They are for the most part secondary, they have no characteristic symptoms, and during life are not recognizable. One child will have convulsions, another somnolence; one will be restless and the other comatose, etc.

Dr. Blaud (of Beaucaire), quoted by Rilliet and Barthez, has described a primary cerebral congestion observed in very young children, and characterized in some cases by sudden and profound sleep, in others by numbness and formication in one of the upper extremities, or a half of the face, or by delirium, restlessness, subsultus, tetanic rigidity, paralyses, and dyspnœa. The disease lasts but a few hours, death by syncope being the usual termination. In brief the symptoms in both primary and secondary congestion are those of pseudomeningitis.

Blaud recommends compression of the carotids for fifty to sixty seconds at a time in cases of excitation with full pulse, injected conjunctivæ, etc. The child should be placed in a well-ventilated room, in a somewhat cool temperature, with its head on a rather hard pillow, and covered with cold compresses or an ice bag.

Cerebral Hemorrhage.—This affection is more rare than in adult age or old age, and is usually secondary. It may be capillary or in foci. In the former case it occurs as small red or black spots on the white ground of the centrum ovale. These dots are small clots which can be removed; they may be in circumscribed groups, or scattered over the whole surface of the section. In the second case there are single or

multiple foci, varying in size from that of a pea to that of a hazelnut or an egg, situated in the hemispheres, the optic thalamus, the centrum ovale, the pons, the cerebellum, etc. We find soft black clots or fluid blood, and perhaps yellow ochre-colored foci the relics of past hemorrhages. At the same time we often find thrombosis of the sinuses and meningeal hemorrhages. Cerebral hemorrhage is not rare in the newly born (obstetrical traumatism), and may occur in scorbutus and purpura in older children. The symptoms are obscure, and there are no well-marked paralyses; we have headache, vertigo, mydriasis, hebetude, coma, convulsions, screaming, agitation, strabismus, contractures. Often the condition is first recognized at the autopsy. Even when the seat of the hemorrhage is well limited it is rare to find an apoplectic seizure followed by paralysis, etc., as in old age. Diagnosis is for the most part impossible. Prognosis is very grave.

Cerebral Excitement.—Some children are, from their cradle, restless, noisy, and insupportable. They sleep badly, turning and tossing, moaning without reason, attempt to get out of bed, and would fall unless protected by a railing or net. Later, when they can walk, they are unable to keep in one place, they wander about, breaking everything that they take hold of. Any opposition to their erratic movements throws them into a rage often exhibited in spasms of the glottis or in convulsions.

At school they cannot pay proper attention, and they learn with the greatest difficulty. Yet some of them are very intelligent, and if they deserve the name of degenerate, it is surely a superior species of degeneracy. It would seem more appropriate to class them among the unbalanced or mental sufferers. In adult life they may turn toward hysteria, epilepsy, or insanity, or they give themselves over to masturbation, and have involuntary seminal losses or incontinence of urine.

The family history will usually show neuroses, hysteria, epilepsy, a neuroarthritic diathesis, alcoholism, or gout.

Internal medication is of little value. Baths at night often induce sleep, especially in very young children; later a wet pack, cold douches, dry friction, and massage are of value. The diet should be carefully watched over, and alcohol and spices eliminated from it. Open air, country life, in fact everything that tends to calm the nervous system and to strengthen the body without exciting the brain should be prescribed.

Neurasthenia.—Some victims of cerebral excitement in early childhood become neurasthenics during adolescence. They are no longer excitable, but torpid, indolent, incapable of intellectual effort. They are backward in their studies, and complain of pain in the head which interferes with their work. I saw a well-grown boy of twelve years

(arthritic, nervous, and almost hysterical father) who for several years had an absolute inaptitude for work, and complained of pains in the temporal region, with insomnia, excitability, and lassitude. Examination revealed nothing but these indefinable troubles. Yet the boy had good reasoning powers and a bright mind, and had a very clear conception of his sensations.

For three years he had to be taken out of school, and pursued his studies with a tutor who carefully parcelled out his hours of work. Bicycle riding was advised, and it worked wonders. Life in the country gave good results. His appetite was fickle, he had dyspepsia, debility of all functions, and great depression of spirit. At about the age of fifteen he found his balance, and recovery was complete.

In such cases treatment consists of strengthening measures, such as dry friction, hydrotherapy, rational diet, country life, and exercise in the open air.

Congestion of the Spinal Cord.—However difficult this condition may be of recognition clinically, there does exist a congestion of the spinal cord and its membranes, just as there is a meningocephalic congestion.

This congestion may be active or passive, primary or secondary. It is active and primary in cases of chilling, over-exertion and overfatigue. It is active and secondary in acute rheumatism, smallpox, eruptive fevers, typhoid fever, etc. It is passive in diseases of the heart or lungs complicated by venous stasis, and in compression of the cord from tumors, tuberculosis, syphilomata, etc. The causes are numerous and varied: blows and falls, cold, masturbation, typhoid fever in its spinal form, eruptive fevers, tetanus, chorea, whooping-cough, convulsions, asystole, etc.

In addition to the chills and the fever the chief symptoms are vertebral curvature and pain, rigidity of the neck and back, paresis of the lower limbs with formication, numbness, cramps and contractures, dysuria, cutaneous hyperæsthesia, etc. These functional troubles are very severe but are usually transitory in their nature, and this lack of stability will serve to distinguish simple spinal hyperæmia from the inflammation and medullary congestion of myelitis.

The prognosis of the disease itself is benign, but it is of course subordinate to that of the initial disease.

Revulsives should be placed on the spinal column as quickly as possible; dry and wet cups along each side, and there should be bleeding in the cervical region (West). Strips of blisters along the vertebral grooves, the actual cautery, etc., have also been suggested. At the same time purgatives should be given, as well as ergot or ergotin, and prolonged tepid baths administered, with inhalations of

chloroform, cold lotions, and stimulating friction. Sometimes the use of sedatives, as bromide and chloral, is indicated.

Spina Bifida.—Under the name of spina bifida or hydrorrhachis is described a hernia of the spinal cord and its membranes with the cephalorachidian fluid, through a fissure in a vertebral arch.

Sometimes several children in the same family will have spina bifida or other malformations, as hydrocephalus, strabismus, club-foot, etc. The pathogenesis is clear to one who understands embryology, and it is evident that spina bifida is an arrest in the development of the spinal column. What is its cause? Lannelongue holds that some ulcerative process has prevented union of the vertebræ. Cruveilhier thought there were adhesions in the membranes of the ovum. Sometimes an exostosis is found projecting into the spinal canal. Other tumors have been observed, such as fibroma, lipoma, angioma. In a recent article, Ballantyne (*Archives de Médecine des Enfants*, February, 1898) has demonstrated the association of spina bifida with congenital uterine prolapse.

The usual seat of the trouble is in the lumbar, or sometimes in the cervical region. I have seen a little girl who had at the same time hydrocephalus and spina bifida of the upper cervical region. The dorsal vertebræ are rarely affected. Spina bifida is usually single, and as a rule is small, although it may be enormously large, and sessile more often than pedunculated. If there is a pedicle it is usually when the trouble is in the cervical region. In form it is round or oval, sometimes flattened or humpy. The skin varies greatly in appearance, being thin in one place, normal in another, thickened, hairy, etc. There is sometimes ulceration of the skin. In one case Kirmisson found a myxomatous mass external to the dura mater. The dura mater may be lacking or present. The fluid, which is serous and clear, is neutral or alkaline and rich in chlorides; it may become thick, bloody, and albuminous. Sugar has been found in it. Sometimes it is in the arachnoid cavity, or outside of the cord, or contained within the medullary canal. In the former case we say that there is external hydrorrhachis, in the latter internal. Finally there may be a meningocele, without medullary tissue in the tumor. Most frequently the cord is included in the sac, in which it describes a curve and is adherent at some one point, or it is inserted on the posterior wall of the spina bifida where it terminates in a single mass or in multiple bundles. Externally an umbilical depression is sometimes seen indicating the point of insertion of the cord. The nerves form loops in the sac or end in it as does the cord. The fissure is rarely limited to one vertebra, but extends to two or three, and is more or less long and broad. The communication between the spinal canal and the sac may become obliterated, leaving a true cyst.

The tumor is median, and opaque or transparent; the skin may break before or after birth. There is usually fluctuation, but there may be induration. At the periphery we can feel the bony projections of the separated vertebral segments. There is partial and inconstant reducibility. Pressure may cause pain, convulsions, and paralyses. An upright position, crying, straining, and expiration increase the size of the tumor. If there are two tumors, pressure on one will swell the other. The same thing occurs if there is hydrocephalus. Sometimes the general health remains good, sometimes there are sensory and motor troubles of the lower limbs, incontinence of urine and fæces, and trophic diseases (perforating ulcer). In some cases there is a fissure in the spine without tumor (spina bifida occulta); this variety may coexist with congenital dislocation of the hip and with club-foot. The course of the disease is variable; the tumor may enlarge and burst, causing a fatal inflammation which extends to the meninges; or a fissure may be produced which allows of the constant dribbling of fluid. It is, however, not uncommon to have the tumor remain stationary; we may even hope for a spontaneous cure by obliteration of the pedicle. Lannelongue has seen such an occurrence.

Diagnosis is as a rule easy, but we must be careful to eliminate certain congenital cysts of the sacrococcygeal region, which, however, are situated lower than spina bifida. Any tumor in the median posterior region of the trunk suggests spina bifida. It is important to differentiate meningocele from myelomeningocele, and from myelocystocele; myelocystocele is situated laterally, while the other two varieties are median.

Tincture of iodine, iodized glycerin (two per cent. iodine and six per cent. iodide of potassium) have been injected into the tumor. So has from 1 to 4 gm. of the Morton solution. Simple or elastic ligatures have given good results. Excision, thanks to antisepsis, now shares the favor given to the preceding methods. It may be simple, or associated with ligature of the bone segments, or with transplantation of a bony segment taken from some animal or from the patient himself. Relapse is possible.

Painful Paralysis in Young Children.—A child walking by the side of an older person and held by the hand, trips and is saved from falling by a quick pull on the arm. If the traction have been too violent the child suffers, cries, and its arm falls inert by its side. The paralysis resulting from this traumatism is usually temporary, disappearing in from eight to ten days. Chassaignac in 1856 called attention to this accidental form of paralysis of the arm. Brunon has recently taken up the subject, and has reported many very interesting observations (1893–95). What especially characterizes this paralysis is

that it appears immediately after the injury; it is at first complete in its nature, and disappears little by little. It is very painful, and the child keeps still to avoid the pain; if he is pinched he moves the arm. The most minute examination of the arm and forearm fails to reveal the slightest injury, even an ecchymosis. The attitude of the limb is the same as in obstetrical paralysis; the arm hangs by the side of the body with the forearm in pronation. In case of fracture, dislocation, or sprain, the cause of the impotence is readily seen; in this case there is nothing to see, and one can only conjecture that there has been some straining of the brachial plexus or paralysis by inhibition. In a case of brachial monoplegia, we should look for luxation or fracture, luxation of the head of the radius, or subperiosteal fracture. Having eliminated these conditions, hysteria is to be suspected. The prognosis is benign, and recovery occurs in a few days. The arm will be sufficiently immobilized by being placed in a sling. If the condition persist, friction, massage, and electricity should be applied.

Astasia Abasia.—Under this name Dr. Blocq (*Archives de Neurologie*, 1888) describes a nervous syndrome characterized by the impossibility of keeping the erect posture and of walking normally, while muscular force, sensation, and the power of coordinating movements in dorsal decubitus are all perfectly normal. If the patient is examined in bed the result is negative, the functional trouble appearing only when he attempts to rise and walk.

An upright position is nearly always impossible (astasia), but although normal walking is also impossible (abasia), the patient can get about either on his knees or on all fours, or by running. Sometimes the inability to stand is so absolute that the patient appears to be paraplegic (paralytic abasia), sometimes the abasia is incomplete, and is accompanied by erratic movements (choreiform abasia), and trembling of the limbs (tremulous abasia). This neurosis comes from hysteria and is seen in later childhood.

Patients with this affection should be isolated; and under treatment by hydrotherapy, electricity, and massage recovery will not be delayed.

The Eye.

Acute Œdema of the Eyelids.—This consists of a sudden and ephemeral swelling of either lid. This affection—which M. L. Gaillard calls "acute idiopathic œdema of the eyelids" (Société médicale des Hôpitaux, November 30th, 1900), M. Trousseau, "arthritic œdema of the lids" (*Presse médicale*, March 6th, 1901), and M. de Spéville, "acute essential inflammatory œdema of the upper lid in children" (*Journal de Médecine de Paris*, August 11th, 1901)—is a disease of later

childhood. It occurs spontaneously in either sex, in neuroarthritic families. It is liable to relapse.

In the morning a child which was perfectly well the day before, has a swelling of the upper or of both lids on one side. The affection is rarely bilateral, but in the relapses it may change sides. The tumefaction may be so great as to disfigure the child and close the eye. The œdema is white and soft, but it may sometimes be red. There is no pain. By separating the lids we see that the eye is intact. The urine is clear, there is no fever, and the general condition is good. In twenty-four, thirty-six, or forty-eight hours the œdema disappears, but it may return several months later. Prognosis is benign.

In a first attack one is apt to think that it is a case of conjunctivitis, but there is no redness, pain, nor secretion. Nephritis is excluded because there is no albuminuria. In some cases the swelling may be so great as to suggest diphtheria or purulent ophthalmia. Urticaria is the affection which most resembles palpebral œdema, but we do not find any evidence of urticaria on the body.

There is little to do except to reduce the diet, give a purgative, and keep the child in its room.

Conjunctivitis from Pneumococci.—To Parinaud (*Annales d' Oculistique*, 1894) belongs the credit of having discovered this form of conjunctivitis. The disease is almost altogether confined to new-born infants and to children. It is contagious. Sometimes it takes on an epidemic character, and spreads among school children. It is most frequently met with in the autumn and in the spring. In a few cases the pneumococci are associated with some other microbe, as the Weeks bacillus for instance.

In the new-born infant the disease appears in the first few days of life, attacks both eyes, and is usually accompanied by coryza or by nasopharyngitis. The weeping and dirty condition of the eye is what characterizes this affection. At the end of a few days there is spontaneous recovery, but occasionally the disease persists on one side and may become chronic, especially if there is any obstruction of the nasal canal. Gasparini believes that it may become complicated by corneal ulcers. In older children the inflammatory process is more active while developing more rapidly (five to six days).

The rapidity of development of the disease, its confinement to the lids and to the conjunctival culs-de-sac, together with the watering of the eye are its chief clinical features. But a bacteriological examination should be made to exclude gonococcal conjunctivitis, or that due to the Loeffler or to the Weeks bacillus.

In the newly born, washing the eye with boric-acid water and smearing a little vaseline on the borders will be all-sufficient. Later, or if the conjunctivitis persists, a few drops of a nitrate-of-silver

collyrium or a 1 : 100 sulphate-of-zinc solution may be instilled. If there is an epidemic in a school, the latter need not be disbanded, but the affected children should be isolated.

Pseudomembranous Conjunctivitis.—There are several varieties of conjunctivitis with false membranes, which cannot always be distinguished by an objective examination.

1. Diphtheritic Conjunctivitis. In the interstitial form the eyelids are swollen, hard, and cannot be everted; grayish and bleeding ulcers are found on their edges and in the angles. The swollen, shining, almost dry conjunctiva does not bleed when scarified at this period. The general condition is bad, with fever, and frequently with the coexistence of diphtheritic lesions elsewhere. A second period of mortification and elimination of the eschars follows. The secretion then becomes abundant and seropurulent. In a third period cicatrices and bridles form (symblepharon). Loeffler's bacillus is found. The cornea is nearly always destroyed by an invasion of microbes (Sourdille), an association of staphylococci and streptococci. According to H. Coppez (Brussels, 1897), it is the diphtheritic toxins which attack the cornea. In treating this form of the disease, we must avoid cauterization, scarification, and all violent measures. We must content ourselves with the application of very hot collyria (40° C. = 104° F.) followed by an application of iodoform ointment 1 : 50. Roux's serum should be injected.

There is another form of diphtheritic conjunctivitis characterized by the formation of a buffy false membrane, without extreme swelling of the lids. There is a marked seropurulent discharge, and the false membrane can be removed with the forceps. Diagnosis is made by the presence of the Loeffler bacillus, and by the coexistence of laryngeal or pharyngeal diphtheria. Treatment is the same as above.

2. Diphtheroid Conjunctivitis. Ordinary pyogenous processes may on the conjunctiva, as in the pharynx, lead to the formation of false membranes. We distinguish a superficial, a deep, and a chemical pseudomembranous conjunctivitis, the latter being due to an abuse of topical applications.

Granular Conjunctivitis (Trachoma).—This is a contagious disease seen more especially in low-lying and damp countries, at the mouths of large rivers, in Egypt, Russia, Holland, and in the Danish Provinces. It is favored by poverty, dirt, crowding, and bad air; if there is a pathogenic microbe, it has not as yet been discovered.

There are two forms of the disease, the papillary and the granular.

Papillary Form.—This is met with in very young children, either following a conjunctivitis or occurring idiopathically. The palpebral mucosa is thickened, the conjunctiva covered with villi, dark red and papillary. The process is a vegetative hypertrophy with more or less

marked catarrh. The cornea and the bulbar conjunctiva usually escape the inflammatory process.

Granular Form.—This is seen only in later childhood, and is characterized by gray, translucent granulations situated at the bottom of the culs-de-sac, and resembling frog spawn. There is watering of the eye, photophobia, agglutination of the lids in the morning, and from time to time acute attacks of catarrh with a purulent secretion. Sometimes the cornea is attacked, and pannus and ulcerations result. Cicatricial tissue succeeds the granulations, the conjunctiva appears whitish and adherent to the tarsus, with ectropion, cicatricial bridles, etc. Valude advises treatment of the acute attacks by opiated irrigations (sterilized water 1000.0, extract of opium 0.1), and cauterization with two to three per cent. nitrate of silver. In the chronic condition, the granulations should be touched with a sulphate-of-copper pencil or with crystallized alum. Corneal complications call for the instillation of a few drops of atropine collyrium (1 to 300), and the application of yellow-precipitate ointment (one per cent.). If the granulations at the base of the culs-de-sac are very large and vegetating, they may be excised or brushed over after scarification. After any of these procedures they are to be washed with a 1 to 2,000 bichloride solution, and cauterized with sulphate of copper.

Tuberculosis of the Conjunctiva.—A particle of tuberculous dust may germinate in one of the culs-de-sac, or pus from a neighboring focus of infection or from the sputum may be carried by the finger or otherwise to the eye. If the lid be everted, we see an irregular, notched, or granulating ulceration. As it progresses the preauricular ganglia are affected. The bacilli germinate on the ball of the eye, where they form a hard, tuberculous nodule. The sclerotic and the choroid coats are gradually invaded, but there is no engorgement of the ganglia. The tuberculous focus must be destroyed by excision or by cauterization, which is not attended by any special difficulty. Unfortunately the child has other tuberculous lesions which cannot be reached directly, so that the treatment of ocular tuberculosis is merely a local one. Tuberculosis of the iris and the choroid, which reveals an infection of the blood, is not amenable to treatment.

Dacryocystitis.—Inflammation of the lachrymal sac, or dacryocystitis, occurs in the newly born and in older children as well.

Dacryocystitis of the newly born. Toward the second week of life a purulent catarrh appears which suggests simple conjunctivitis. The appropriate treatment for that affection, however, gives no result. Pressure on the lachrymal sac brings pus, and the disease is seen to be a catarrh of the lachrymal sac, without marked swelling and without involvement of the nose. Examination of the pus reveals the pneumococcus as a rule. In a child born with a lacrymal tumor (3

or 4 c.c. or pus), Valude found a tetragenous microbe. In the case of another who had a very apparent double dacryocystitis, he elicited a history of hereditary syphilis. The dacryocystitis of the newly born is not very grave, and is rapidly cured by the insuring of the permeability of the lacrymal passages. If mechanical evacuation of the sac and instillations of a 1 to 100 sulphate-of-zinc solution do not bring relief, incision of the puncta lacrymalia and catheterization must be resorted to.

Dacryocystitis of Later Childhood. This affection as a rule is dependent on scrofula, caries of the bone, etc. There are no acute symptoms, nor is there preëxisting conjunctivitis. At the root of the nose a tumor of greater or less size is seen. Pressure causes the oozing of pus or of a gummy substance from the puncta lacrymalia. The skin may become inflamed and an apparently inexhaustible lacrymal fistula forms, from which for a long time issues a flow of pus and of tears. The disease is graver than it is in the newly born. The lacrymal canals must be freely incised and catheterized, and the cavity washed, curetted, and cauterized. Treatment is often extremely difficult. The general condition must not be neglected, and cod-liver oil or preparations of iodine should be given.

Foreign Bodies in the Eye.—Nothing is more usual than to find foreign bodies in the eye—dust, tiny insects, bit of grain, of metal, etc. Relatively large bodies may lodge in the culs-de-sac where they hide behind inflammatory granulations of the mucosa. The children are carefully treated for conjunctivitis until the idea suddenly occurs that there may be a foreign body present, and it is sought for and extracted. The lids must be everted, which is not always easy on account of blepharospasm and indocility on the part of the child. After extraction of the foreign body, antiseptic washings and cold compresses should be applied.

Foreign bodies which lodge in or go through the corneal walls, whether they remain in the eyeball or only perforate it, may be followed by very grave consequences. In addition to infection, we have to think of the possibility of adhesions of the iris. Should the wound become infected, the cornea and the anterior chamber will become cloudy; hypopyon may follow, or perhaps a purulent ulcer. If that be the case, disinfection cannot be too carefully done. Should there be phlegmon of the eye, the globe will have to be opened and even enucleated. If a small foreign body is encrusted in the cornea, it can be removed by means of a needle previously passed through the flame.

Cataract.—The crystalline lens loses its transparency, and has grayish-white opacities on its surface, or else a dark central nucleus. By dilating the pupil with atropine we can estimate the degree and the

shape of the cataract. There are constant visual troubles. In the central or in the lamellar cataracts vision is diminished, and the child sees better in darkness which dilates its pupils. There are several varieties of cataract.

Congenital cataract. Lamellar cataract, the most usual form, occurs as a gray, translucent round opacity, distinctly separated from the periphery; the pearly gray color is more marked at the periphery than toward the centre, and the equatorial portions of the lens are transparent. If the cataract is small and central intervention will not be necessary; should it be of larger size, while still permitting vision under atropine, an iridectomy upward and inward must be performed, while in case of very large central nucleus, there must be extraction.

Anterior or posterior polar cataract is very rare, and is to be treated by iridectomy.

Soft congenital cataract is of easy recognition from the milky white aspect of the lens; it should be operated on.

Acquired Cataract. A soft, simple cataract may occur in albuminuria and in diabetes, and after a while may become calcareous.

Soft cataract is easily cured by puncture. Traumatic cataract follows a wound of the cornea (from pen-point, knife, or scissors) which reaches to the lens. The lens very rapidly becomes opaque. The cataract is of the soft variety. No treatment is to be applied until the inflammatory or infectious symptoms have subsided. Recovery may be spontaneous. Operation presents no difficulties. Pathological cataracts (following iridocyclitis), observed in advanced disease of the eye, are to be left untreated.

Glaucoma (*Hydrophthalmia, Buphthalmia*).—Glaucoma consists of an increase in size of the eyeball. There is intraocular tension with swelling of the sclerotic, either spontaneously or as a result of destruction of the cornea and incarceration of the iris. In the primary form, there are symptoms of ciliary irritation, of cyclitis. The aqueous humor becomes cloudy, the anterior chamber deepens, the ocular tension increases; the sclerotic forms a ring of protuberances around the cornea (intercalary staphyloma), or else the whole anterior segment is pushed out *en masse*, the whole eye being enormous, and the iris dilated; vision is diminished because of the deep lesions and the convexity of the eye. The vitreous body is cloudy, the choroid is affected, and sight is threatened.

The treatment of glaucoma after incarceration of the iris consists in the instillation, from the very onset, of a one-per-cent. solution of eserine, in the internal administration of phosphate of lime, and, if necessary, in iridectomy. In the primary glaucoma of later childhood, sclerotomy, minute puncture of the sclerotic, should be performed to diminish the intraocular tension. In the case of arthritic or rheu-

matic children, general treatment should be instituted, consisting of sodium bicarbonate, sodium salicylate, or the benzoate of lithium.

Cancer of the Eye.—Cancer of the eye is rare, but it may be observed in the first months or first year of life. Sarcoma is the form usually met with, as is the case in all tumors of childhood. If the eye is affected suddenly, it is as a rule glioma of the retina that is observed. The pupil takes on a whitish aspect, and appears to shine like a cat's eye in the dark. Vision is abolished. By oblique light we perceive a cottony, nodulated, vascular mass. The tumor grows, invades the entire eyeball, and extends beyond it to the cavity and walls of the orbit. It may attack the optic nerve and penetrate into the brain, or else project forward under the eyelids. The other eye may be affected through the optic chiasm.

There may be sarcoma of the orbit which originating outside of the eyeball soon compresses it, pushes it one side, and causes it to project, while with terrible rapidity the neighboring sinuses are invaded.

Sarcomata of the eye and orbit in young children are extremely malignant. In spite of the danger of a relapse, it is impossible to remain inactive in the presence of such a growth. As soon as the diagnosis is made, the affected eye should be enucleated, the orbit cleared out, etc. But we must be sure of the diagnosis, bearing in mind that tuberculosis of the iris in its fungoid, perforating form can simulate cancer of the eye.

Tuberculosis of the Iris and Ciliary Body.—Ocular tuberculosis is usually situated on the iris, and its study is of the greatest clinical interest. It is a disease of childhood—of later childhood as a rule, but also of infancy. Primary infection through the conjunctiva is rare, tubercle of the iris being as a rule secondary to tuberculosis of the mediastinal or the pulmonary glands. Like other forms of surgical tuberculosis it is hæmatogenous.

There are several forms of the disease. In some cases there is a solitary unilateral tubercle (granuloma of von Graefe), which may or may not be accompanied by small miliary tubercles, and simulates a neoplasm, without acute reaction, without iritis, and may go on to recovery. Sometimes small gray nodules are seen on the iris, which after a while disappear to be replaced by others, or which may heal, or become caseous, or destroy the anterior segment of the eye; these tubercles are situated near the attached margin of the iris (Van Duyse), or may be on the ciliary body to the exclusion of the iris. In some cases there are no tubercles, merely the symptoms of a serous or a plastic iritis.

We see an attenuated form, susceptible of spontaneous cure, and a grave, suppurative, and destructive form; in the latter the tubercles increase in size, fill up the anterior chamber, emerge beyond (fungus),

and distend the sclerotic (intercalary staphyloma). Sometimes, but rarely, there are symptoms of acute glaucoma. Although spontaneous cure is a possible thing (child of five years, reported by Wecker), the danger is very great for the functional power and the existence of the eye, and for the general condition of the child.

Diagnosis is very difficult. Hereditary syphilis, sarcoma, rheumatic iritis, and panophthalmia are all sources of possible confusion. All of these errors have been committed and corrected by enucleation. Tuberculosis of the iris is not sufficiently taken into account, not being considered as frequent in childhood as is really the case.

If syphilis is suspected, mixed treatment should be tried (mercurial frictions, iodide of potassium). The eye is not to be enucleated. Iridectomy is usually all that is necessary; de Wecker performed this operation on a child of five years, and seven years later had the opportunity of noting that it was in good health and had perfectly good eyesight. Iridectomy is especially valuable in cases of solitary tubercle. If there is disseminated tuberculosis, Pechin advises abstention from operation, there being danger of hastening the course of the disease by operatory traumatism. In short, conservatism is to be practised in tubercle of the iris, and medical treatment carried out by means of fresh air and rest, good feeding, cod-liver oil, etc.

SCARLATINA.

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THE following consist of additions to, and, in some instances, corrections of, statements made in the original article.

Predisposition.—Seitz has collected eight hundred cases, occurring in the polyclinic at Munich, from which he draws the conclusion that the number of cases is independent of the time of year and of the character of the weather. While this does not agree with the statements made by various authors (Hirsch, Criger, Johannessen, and my own statistics for Berlin), it further illustrates the conclusion arrived at in the original article that for the present "deductions cannot be made with any reasonable degree of assurance" as to the effect of season upon epidemics of scarlet fever. Family predisposition, referred to by many authors, is distinctly brought out in these statistics. Out of the 800 cases there were 429 single cases; the remainder, 371, being found in 152 families. As 80 cases out of the 429 could be thoroughly isolated, Seitz comes to the conclusion that the ratio of single to multiple cases in the same family is as 349 to 371. The cases of multiple infection are arranged as follows: Scarlatina occurred 108 times in 2 members of one family, 31 times in 3 members, 3 times in 4 members, and twice in 5 members of one family.

He also shows a temporary predisposition in that in 62 groups of cases, with 150 patients in all, the disease broke out at the same time or within one to two days after exposure, while in 90 groups, with 221 cases, the disease broke out in from one to six weeks after possibility of infection had existed, *i.e.*, with constant or repeated exposures; thus in two instances the nurses became infected after being exposed for from three to five weeks. It is possible that other factors besides the one of temporary predisposition might have figured in this result; it must be remembered that positive knowledge of the cause of scarlatina is wanting, so that this factor cannot be neglected; and, furthermore, the mode of infection may be responsible for at least some prolongation of the period of incubation.

Max Hirsch, reviewing 393 cases in the Charité Hospital in Berlin, verifies the above as follows: Scarlatina occurred 47 times in 2 members of one family, 15 times in 3 members, 3 times in 4 members, twice in 5 members; 41.2 per cent. being multiple cases in one family.

McCollom shows that the morbidity rate of scarlatina in Boston varies from 16.77 per 10,000 (1898) to 62.87 in 1892. He draws the conclusion that this enormous reduction in morbidity is greatly due to the establishment of a contagious disease department in connection with the Boston City Hospital. It is astonishing to see the great mortality and morbidity of Boston, as in 1893 it exceeded that of London, Liverpool, Glasgow, or Berlin, all places renowned for the prevalence, and therefore mortality, of scarlet fever.

Bacteriology.

In discussing this subject before, the author made the statement that up to the year 1896 the specific organism of scarlatina had not been found; but that on account of the frequency with which streptococci had been found (Klein, Babes, Fiessinger, Berger, D'Espine, Marignac) "it will not be strange if finally a specific streptococcus" be found. Since this time two notable contributions have been offered in connection with this subject: the first by William J. Class, of Chicago, in which all the requisites of Koch have been fulfilled by the discoverer, and, therefore, of great promise as to its value. Class (1899) in examining 700 to 800 throat cultures found large diplococci as well as other bacteria; he noticed that the former were most frequently present in cultures from the throats of scarlet-fever patients, but failed to isolate and cultivate them until he took a medium made up of agar and five per cent. of garden soil. Class describes the germ as a diplococcus, polymorphous in character, resembling a large gonococcus, best seen in faintly stained specimens. Tetrads are quite common, and in old cultures a slightly cupped, enormously large coccus is found, sometimes also a crescentic form. By division smaller organisms are produced which do not appear as diplococci during this stage of growth. Streptococcus forms are rarely found, and the cocci usually arrange themselves in groups of from ten to fifty. The organism has no capsule; there are no spores, and it is immobile. It is best stained by aqueous solution of methylene blue, carbol fuchsin, Bismarck brown, or Pittsfieldt's flagella stain, and is decolorized by Gram. Fresh cultures do not stain well. In scarlatina Class has succeeded in making cultures from the skin during desquamation in 74 cases, from the throat in 50 cases, and from the blood in 16 cases. The organism grows also upon blood serum and glycerin agar, losing many of its characteristics, but does not grow upon gelatin, nor upon

milk, only multiplying in the latter medium. He found it in 8 out of 36 cultures from the throat of healthy subjects, in 3 out of 30 cultures made from healthy skin (dandruff); never in the blood of healthy subjects, "almost invariably" in the blood of scarlatina patients. It is not pathogenic for rabbits and guinea-pigs; in the latter immunity may be overcome, and then nephritis is produced. It is pathogenic for swine (*sic!*). Injected into the veins it produces fever, an eruption and desquamation, and the organism was found post mortem in the animals in the skin and the nephritic kidneys. Plate cultures can be made only in a peculiar way, because heat destroys the organism. In a second paper (1900) Class found the organism in the throat of 300 scarlatina patients; in 212 cases with all the manifestations of scarlatina, and in 88 cases of scarlatina sine exanthemate. He also found it in about 20 per cent. of all cases of acute amygdalitis. Furthermore, he now finds it pathogenic for gray mice, and shows the inhibitory action of blood from scarlatinal patients upon its growth. In a third paper, he finds that guinea-pigs die in from one to two weeks when a virulent, pure culture is injected into the abdominal cavity, and that this can be prevented by the use of an antitoxic serum, prepared in the usual way from the blood of swine. As a result of these three papers he claims to have established (1) that the organism is always present in scarlatina; (2) that it is found in animals during life and post mortem; (3) that it can be cultivated outside of the body; (4) that when inoculated in pure culture it produces scarlatina and its pathological lesions; (5) that a toxin is produced which kills mice. Jacques verifies Class' statements as to the specificity of the organism; he has found it in scarlatinal sore throats with the same regularity that he has found the Klebs-Löffler bacillus in diphtheria. Gradwohl agrees to the specificity of the organism; he has obtained it in pure cultures from the blood and urine; he finds it pathogenic for mice, guinea-pigs, and swine; not pathogenic for dogs, cats, white mice, and rabbits. The disease produced in mice is contagious for other mice. He confirms Class' results in guinea-pigs and swine, and adds that the organism is a facultative anaerobe whose thermal death point is 49° C.; optimum temperature for growth 36° C., and the growth limits 18° to 39° C. Page makes the statement that in scarlatina he has found an organism corresponding with the description of the diplococcus scarlatinæ.

Baginsky and Sommerfeld have published two articles on the subject of the bacteriology of scarlet fever (1900 and 1902), the last one to be referred to in detail. They found in 411 cases of scarlatina streptococci associated with other lower forms of life; in 22 cases the Klebs-Löffler bacillus associated with the streptococcus; 138 cases were examined by culture—bouillon, plate culture, blood serum, or

agar-agar; in them the streptococcus alone was found in only 4 cases. There were various kinds of streptococci, which were found *intra vitam* in the spinal fluid, the urine, and the blood; post mortem in the blood of the heart, the marrow of bones, the lungs, the spleen, the liver, the kidneys, the bronchial and mesenteric glands, and in the contents of the gall bladder. The streptococcus referred to by the author was found in almost pure culture in these localities, unless the autopsy was deferred too long after death. The morphological characteristics of this lower form of life are: It forms chains of variable length and size of cocci, sometimes in the form of tetrads. In bouillon the length of the chains varied from three to fifty cocci and more. The coccus is usually round, sometimes flattened in the direction of the axis of the chain, so that two lie next to each other; when stained, the individual links make the impression of diplococci. By changing media the diplococci and short chains can be converted into long chains, and these can again be converted into short ones—a common characteristic of streptococci. The bacterium stains with all aniline dyes, especially carbol-fuchsin, but is not decolorized by Gram. For the purpose of determining cultural peculiarities they have tested twenty media, including that of Class, with negative results. Upon using Class' medium no peculiar appearance of the culture was observed, nor did they find forms resembling gonococci. Inoculations in rabbits, which were especially susceptible to their germ, showed neither uniformity of result nor dependence upon the original source of the germs as to virulence. By successive inoculations there are produced increased virulence and sepsis. The streptococci were not agglutinated by blood from convalescent scarlet-fever patients. By injecting pure bouillon cultures plus serum from convalescents, life was prolonged in two instances; in four other animals the result was negative. Five animals were killed by injections of the toxin. The streptococcus was found in the pharynx of human beings and post mortem in fifty-eight septic cases. The authors do not as yet feel justified in claiming this streptococcus as the specific organism of scarlatina, but add to the title of their paper the clause that it is "a constant bacterial condition in scarlatina." If this were all, it would be nothing new, as English and French observers have repeatedly stated the same: the paper consists of a most careful bacteriological study of a polymorphous streptococcus which was found in all the cases examined by the authors. After the publication of Baginsky and Sommerfeld's first article, Class made the statement that these authors had not taken the trouble to read his papers, and that they had quoted an editorial article of the London *Lancet*, otherwise "they would not have failed to notice the similarity in many particulars of this germ [his diplococcus scarlatinæ] with the one whose discovery they announce." In Baginsky and Sommerfeld's

second article this objection falls away as they mention Class' culture medium, and fail to verify his results. It is true that they have not followed his methods in many ways, and have not prepared the culture medium as he directs it to be prepared. Aside from the occasional similarity of appearance of the polymorphous streptococcus and Class' diplococcus, the author fails to see how the German writers have verified Class' discovery; and indeed, he fails to see that they have thrown any new light upon the etiology of scarlet fever. On the other hand, Class' diplococcus has been verified by at least three other observers, and its existence has been neither proven nor disproven by the work of Baginsky and Sommerfeld. So that for the present the evidence is distinctly in favor of the existence of Class' organism. It would be very desirable, on account of the therapeutic outcome, if for no other, that the whole subject should be definitely worked out on the lines drawn by Class and according to his methods.

Pathological Anatomy.

Some very important investigations have been made in connection with the pathological changes in scarlatina. First and foremost are those made by Councilman and some of his pupils. Councilman has devoted himself especially to the kidney, and in his studies has thrown great light upon the pathological anatomy of the scarlatinal kidney. He does not confirm the view that the essential lesion in scarlatinal nephritis is a glomerulonephritis, but believes that the most common form is that of acute interstitial nephritis, a statement more positively made by Pearce, who says that in the scarlatinal kidneys examined by himself "acute interstitial nephritis was the most important lesion." Baginsky repeats in a second paper the statements made by himself and Stamm in 1893: 1. That in children dying of scarlatina, during the first week of the disease (principally septic cases), there is an interstitial nephritis, either diffuse or confined to the blood-vessels; both the glomeruli and the Malpighian bodies participate in this process, but here neither exudative nor degenerative processes are found. 2. In the second week, also principally septic cases, the same process, plus degenerative changes in the epithelium of the convoluted and straight uriniferous tubules, is found. Nothing of especial importance is found in the Malpighian capsule or tuft. 3. In the third week only marked changes are found in the glomeruli, in addition to degenerative changes in the epithelium and the interstitial changes, as noted before. He states that "scarlatinal nephritis can by no means be considered as primarily or simply a glomerulonephritis." This, on the whole, seems to be the opinion of both Councilman and Baginsky, and the view that scarlatinal nephritis is always a glomerulonephritis may

have to be changed, or, better, we shall have to accept the view that scarlatinal poison does not produce a specific form of kidney lesion, different from the one produced by other infectious diseases. As against this latter view the clinical evidences must be arrayed, which, however, would be of little value when not verified by pathological findings. At present neither acute glomerulonephritis nor acute interstitial nephritis can be looked upon as *the* form of scarlatinal kidney, as both of them occur in so many other diseases; but the evidence at present seems to be in favor of the greater frequency of the latter form.

In connection with the skin lesion it is of interest to determine whether we are dealing with a dermatitis, as stated by Hebra and Kaposi, or a vasomotor process, not a true inflammation. Pearce has examined the skin in eight cases between the second and sixteenth days of the disease, and in one case on the thirty-second day. Barthez and Sanné's point, that the disturbance begins in the lymphatics and only secondarily affects the blood-vessels of the skin, is not settled by this author. The changes observed by him in the skin were as follows: On the second day only congestion of the blood-vessels and slight dilatation of the lymphatics are found; on the third day, besides this, a few leucocytes and lymphoid cells are found within and around the lymphatics beneath the rete Malpighii; from the fifth to the tenth day the most marked change is an infiltration of the rete Malpighii, with polymorphonuclear cells; these are thrown off with the desquamating epidermis, together with leucocytes and red corpuscles. The connective tissue beneath the epithelium contains polynuclear leucocytes and a few plasma cells, and the lymphatics are overfilled with leucocytes. From the twelfth to the sixteenth day the leucocytes have nearly disappeared, but small collections of round cells are beginning to appear around the blood-vessels and lymphatics of the corium; these were very well marked in the case that ended fatally on the thirty-second day. Practically the same condition is found in the tongue, except as modified by functional differences and locality, and the conclusion arrived at by Pearce is that the condition of skin and of mucous membrane is "not merely vasomotoric, but also inflammatory." In his general summary the author states that the only constant change in scarlatina is hyperplasia of the lymphoid tissue in every part of the body. He here verifies the statements made by a number of clinicians; Hawley even proposed that the name of the disease should be changed from scarlet to lymphatic fever. To quote from Pearce, the most important inflammatory complications observed in these cases in the order of their frequency are: Acute bronchopneumonia, acute inflammation of the middle ear, with or without extension to the mastoid cells, suppuration of cervical lymph nodes, acute pleuritis, and inflammation of

the antrum of Highmore. The less frequent complications are abscess of the lung, ulceration and abscess formation in the upper respiratory tract, acute endocarditis, inflammation of the splenoidal sinus, and metastatic abscess of the kidney. In the gastrointestinal tract he found "degenerative changes in the epithelium" and proliferative and degenerative processes in lymph nodes, similar to those in lymphoid tissue elsewhere. In the heart muscle were found fatty degeneration and fragmentation. The changes in the liver and the spleen were the same as those found in all other acute infectious diseases, except as to their lymphatics. He reports what has been referred to before in connection with the changes in the kidney, but says that glomerulonephritis was not found because the patients had died too early in the course of the disease.

Symptomatology and Complications.

It is gratifying to be able to verify the fact that the eruption upon the mucous membranes, the enanthem, is receiving more attention at the hands of recent authors. It may be necessary to state that the term enanthem, as applied to the acute exanthemata, includes all of the manifestations observed upon mucous membranes. Since the original article was written various contributions have been made upon the subject of enanthems; Koplik's spots in measles; the author's description of the enanthem of rubella, refered to in the article on rubella in this work, but published in detail afterward, and finally, an accentuation of one of the peculiarities of the tongue by McCollum. All of these are valuable for the purpose of differential diagnosis. Indeed, no examination of a patient with a rash is complete without an examination of the mouth and throat; furthermore, in some cases of the eruptive fevers the enanthem is all that is to be seen of the eruption. In this connection attention must be called to the absence of enanthems in rare cases of the acute exanthemata; they are rarely entirely absent, but sometimes delayed, and then the diagnostic value of the enanthem is greatly diminished. In scarlatina the enanthem is of value for both diagnostic and prophylactic purposes. McCollum lays much stress upon the enlargement of the papillæ at the tip and edges of the tongue, stating that "this enlargement is a constant symptom in scarlet fever, and has not been absent in any of the one thousand cases observed. It has formed the basis of the diagnosis in many of the doubtful cases. A positive and correct diagnosis of scarlet fever sine eruptione can only be made from this symptom." This statement is too comprehensive in that, as he even says, "a faint eruption could be seen in the throat which is always congested," and in that this enlargement of the papillæ may be found in other conditions besides scarlatina. The author would look upon this manifestation simply as a part of the

enanthem, possibly as the most rudimentary form of enanthem, for while the enanthem begins at the tip or edges of the tongue, it rarely is limited to these places, but develops all over the tongue, as described in Vol. XIV., pp. 38, 41. It is probably first developed at the tip and edges of the tongue, because of local predisposition, the result of mechanical irritation.

The *enanthem of rubella*, which has been observed by a number of authors—American, German, and French—is of importance principally in that it helps to establish rubella as an independent morbid entity. For diagnostic purposes it can be utilized only under the most favorable conditions, as they occur in civil practice principally, and by careful observations made upon the healthy children of a family in which German measles has developed. In order to discover this enanthem children must be seen at least twice a day, better oftener, because it is very short-lived; for these reasons this enanthem has been overlooked by some authors who deny its existence.

Koplik's spots are of great importance in all directions, but not more so than the general enanthem of which they are only a part. It is even possible that they appear a few hours before the enanthem appears upon the soft palate, a fact by no means established. The author has been in a position to observe an epidemic of measles in which the reverse was the case in a majority of the patients. Koplik's spots have the characteristic bluish color of the whole enanthem; they are developed especially upon the inner surface of the cheeks, having a whitish centre, probably due to degenerative changes in the epithelium, and first noticeable opposite the last lower molar tooth. Aside from all questions of priority, Koplik deserves great credit for his careful observations and for having insistently called attention to this part of the enanthem, thus introducing the whole subject to the medical profession at large.

Complications.—Pearce's view as to the frequency of pneumonia in scarlatina must be looked upon as the result of purely local conditions. Certainly the author's experience does not carry out this view. With him pneumonia is an exceedingly uncommon occurrence in scarlatina. Even in Seitz's ambulatory material it occurred in only 1 per cent. of the fatal cases; so that in private practice the morbidity, even in Munich, must be much smaller. Seitz states that 6.3 per cent. of his cases had pneumonia; 5.2 per cent. bronchitis; 5 per cent. myo-, endo-, or pericarditis; 3.8 per cent. gastrointestinal diseases; 23 per cent. nephritis, and 12 per cent. lymphadenitis. In connection with nephritis he asserts that its frequency has no relation to the time of year, to family predisposition, to catching cold, or to diet. With his material it was impossible to keep the children in bed or to diet them (including the impossibility of preventing beer

drinking), yet in winter only 9 per cent. of all cases had nephritis, while in summer 41 per cent. had this complication. His experience with milk diet was not satisfactory, yet he would not neglect every possible precaution, including rest and diet, as he believes both chronic nephritis and the cyclic albuminuria of puberty to be the possible result of such neglect.

Treatment.

We are unable to state that much progress has been made since the publication of the original article. Therapeutic results obtained by the injection of serum obtained from the blood of convalescents (Huber and Blumenthal) may be referred to, and Leyden again writes upon the same subject, having since that time added three new cases. As a matter of fact, all of the fifteen cases (twelve Huber and Blumenthal, three Leyden) did very well: the fever curve was somewhat changed from the average one; there was no nephritis, but in three cases other complications occurred. The tone of Leyden's paper is optimistic to a degree, and possibly the great clinician may be justified in his optimism; but, if any disease requires caution in drawing therapeutic conclusions, it is scarlatina, especially when deductions are drawn, as in this instance, from fifteen cases, principally adults, as it is a well-recognized fact that the mortality from scarlatina beyond the tenth year of life is very small. But disregarding these objections, the method itself is open to severe criticism. It is an open question whether the injection of alien human blood into a patient would not eventually be followed by greater morbidity, and possibly mortality, than scarlet fever itself. Until some other method of producing scarlatina serum is found most physicians will hesitate to use it.

Seibert has recurred to the specificity of inunctions, first recommended by Schneemann and taken up by many authors, each one finding some specific, which is added to the simple ointment. Seibert recommends ichthyol, from which (ten per cent.) he has obtained good results. The indications for the use of ointment have been discussed in the original article, and nothing has been done to cause a change of opinion on this subject.

For symptomatic treatment also very little has been added. The streptococcus serum has proved a failure, likewise the unguentum Credé. The latter is, however, serviceable in some local suppurations; the author has been signally successful in the prevention of cellulitis in connection with cervical adenitis; incisions were made into the subcutaneous connective tissue and the salve was introduced into these. In one case the process was abortive. Iodovasogen has been highly recommended in the tumefaction of glands.

The question of milk diet has been negatively answered by a large

number of European authorities. Disregrading all experiments upon human beings and admitting that nephritis cannot be prevented by putting every patient with scarlatina upon a milk diet from the onset of the attack, the author still claims that, theoretically as well as practically, the treatment of nephritis with milk diet is an ideal one. It has been claimed that gastro-intestinal disturbances are produced by this method; that a sufficient number of calories is not provided for, and, lastly, that the method is not easily carried out. Gastrointestinal troubles are not of common occurrence. When this is the case, modifications of milk with lime water, gruels, carbonated water, cocoa, etc., or predigestion-milk may be used. The number of calories depends entirely upon the quantity of milk taken. A quart of milk equals about 590 calories. It is very easy to give a child two quarts of milk (1,180 calories) in twenty-four hours, sufficient in most instances to produce a gain in weight. If the latter is not accomplished or the patient loses weight, simple carbohydrates, as strained oatmeal, rice, arrow root, or cocoa may be added, which will obviate these difficulties. In a long experience the author has found a certain number of patients in whom the taking of milk seemed to be impossible; for such egg or vegetable albumin may be substituted for the milk albumins; these, with the addition of carbohydrates, make an efficient substitute for simple milk diet. Under all circumstances the indication in nephritis is to rest the kidneys as much as possible by the introduction of non-irritant substances. No one can claim, in the present condition of our chemical knowledge, that the results of meat nuclein decomposition are non-irritant, while those of vegetable albumin and milk albumins (paranuclein) are distinctly so.

THE DISORDERS OF MENSTRUATION.

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THE subject of the disorders of menstruation, could it here be adequately treated, would in reality cover the entire domain of gynæcological pathology, but it is the writer's intention to limit his remarks to certain subjects, not, perhaps, quite fully discussed in the seventh volume of this work.

Retention of the Menses.

Retention of the menses is produced by an accumulation of more or less altered blood in the vaginal canal. This phenomenon is quite as rare as suppression of menstruation is frequent. In one case ther is a complete arrest, due to a cessation in the production of the menstrual discharge. In the other the production of the liquid element still persists. The blood continues to leak through the uterine mucosa, but cannot escape outwardly, because either there exists an atresia of the uterus or obstruction is present at some point of the vaginal canal.

Acquired or congenital atresia of the genital canal is the cause of the retention of the menses, and the site of obstruction may be the hymen, in the vagina, or in the cervix uteri.

Just as there may be a hæmatrometrium or a pyometrium, so may we find a hæmatocolpos or a pyocolpos, a hæmatosalpinx or a pyosalpinx, according to whether the retention of the menstrual blood arises in the vagina or in the tubes. This retention will always give rise to a tumor, which is more or less painful, fluctuating, and elastic, and produces symptoms of vesical and rectal compression. A high temperature, a rapid pulse, very severe pain, localized at a certain point of the tumor, should always give rise to the suspicion that a suppurative process has become added.

The liquid found in retention of the menses is a chocolate color and mucoid in nature, and if examined microscopically will be seen to

contain altered blood pigment in the midst of epithelial cells and deformed globules.

The treatment simply consists in the evacuation of the sanguineous cyst. When it cannot be reached per vaginam, abdominal section is obligatory, followed by extirpation of the uterus and tubes.

Amenorrhœa.

Amenorrhœa may be defined as a permanent or temporary absence of the menses occurring at the time of life when they should be present. The cause of amenorrhœa may exist in the patient's general condition or in a pathological state of the sexual organs.

Among the most frequent general causes of amenorrhœa may be mentioned constitutional diseases which produce anæmia and changes in the normal composition of the blood, such, for example, as Bright's disease. Diseases of the circulatory system are also prone to influence the menstruation, and tuberculosis, by its weakening effect and the denutrition that it produces on the system, may also be considered a potent factor. Chlorosis often accompanies amenorrhœa in young subjects. This disease usually appears at the age of puberty, and at this time only on account of the increase of work demanded by the nutritive and circulatory systems for the development of the sexual organs. A frequent cause of amenorrhœa is neglect of proper hygiene at the time of puberty—bad air, insufficient nourishment, overwork, want of exercise. Amenorrhœa frequently occurs after scarlatina and pneumonia, but under these circumstances, when convalescence has become fully established, the menstruation will take place.

A much more frequent cause of amenorrhœa is the incomplete development of the uterus or ovaries, or both these organs. When an arrest of development arises in all the organs composing the genital system in the female, the subject will remain in most instances small and infantile, although occasionally the woman may take on a masculine appearance. In some cases the uterus, vagina, and tubes are rudimentary in development, but the ovaries are normal, and in these cases the woman may possess all the appearances of her sex, and a local examination is required in order to recognize the deformity.

In order to be of some value, the treatment of amenorrhœa should be instituted after an exact diagnosis of the cause has been made. The inconsiderate use of emmenagogues may be without effect in causing the return of the menstrual flow, or it may provoke a loss of blood, which will only aggravate the anæmia present in the already weak patient. As to the amenorrhœa which accompanies or follows acute diseases, little or no attention need be paid to it, as after the cure of the affection menstruation will occur.

Young anæmic women of rapid growth, whose sexual development is delayed, should be ordered a life in the open air, avoidance of fatigue, and some digestible preparation of iron combined or not with arsenic. Particular attention should be paid to the intestinal tract in these subjects, as they in almost every instance suffer from intestinal toxæmia, and to combat this a pill of 0.05 each of oxgall and extract of cascara will be found very serviceable. The pills should be given twenty minutes after each meal, and the result will in most cases be very satisfactory.

The stimulating effect of the faradic current may be essayed as soon as the blood shall have acquired a sufficient richness in hæmoglobin, and when the muscles have become well developed, weak emmenagogues, such as permanganate of potassium, in doses of from 5 to 10 cgm., may be found of service.

If amenorrhœa is due to a delay in the development of the genital organs, and the patient is not more than eighteen or twenty years of age, the faradic current may be employed to advantage, and the exhibition of iron combined with aloes may be indicated. All operative procedures directed to the cervix or the cervical canal are, in my opinion, unwarrantable and unjustifiable.

And lastly, if the patient is in other respects in good health, a happy marriage may be the best stimulant for the regular development of her sexual organs. It should nevertheless be remarked that with these women the menopause is often early in its appearance, and that the first pregnancy may result in a miscarriage, although the possibility of normal labors in the future is not at all unlikely.

In considering *dysmenorrhœa* there are two types to be distinguished. The first may be termed idiopathic, and is independent of any lesion of the genital system, while the second, which I would term secondary dysmenorrhœa, is produced by some lesion of the tubes, ovaries, or uterus. I would nevertheless point out that these two types are so similar in their general characters, appearance, and progress that they should be regarded as belonging to the same family.

In all women at each menstrual period there is an intermittent contraction of the uterus, perhaps provoked by what Fritsch has termed the premenstrual swelling of the uterine mucosa, but more especially by the menstrual blood, which acts as a foreign body in the uterine cavity. This menstrual contraction of the uterus, which in women mentally and physically well is painless, becomes a dysmenorrhœa under certain conditions.

In those cases of functional disturbance of the nervous system which are supposed to be related to hysteria or to neurasthenia, even when the genital system is absolutely healthy, we have the so-called nervous dysmenorrhœa, which, I believe, we may consider simply a

stigma of hysteria. In a second class pathological changes of the genital canal have taken place, such as malpositions, strictures, and occlusions, creating an obstacle to the flow of menstrual blood, and from which results an exaggerated uterine contraction, which is painful even for a healthy nervous system. This we may term mechanical dysmenorrhœa. It may coexist with the neurotic dysmenorrhœa. In the third class we would include those cases in which there is a pathological change in the pelvic organs, accompanied by an increased sensibility of the genital organs as well as the neighboring viscera, so that the menstrual uterine contraction, even although not exaggerated, becomes painful. This may be termed inflammatory dysmenorrhœa.

We have many facts which well demonstrate that dysmenorrhœa is simply a painful menstrual constraction of the uterus. The pain of dysmenorrhœa quite closely resembles labor pains, but the latter depend, just as does the pain of dysmenorrhœa, on the size of the obstacle to be overcome and the condition of the central nervous system. The pains of dysmenorrhœa, when the genital organs are normal, are often met with only at the beginning of the menstrual flux, and they cease as soon as the blood has triumphed over the obstacle produced by a plug of mucus in the cervical canal. A violent dysmenorrhœa is often met with in young girls and nulliparous women who have a narrowed internal os.

Mechanical dysmenorrhœa, as well as inflammatory dysmenorrhœa, can be cured only by a removal of the cause.

Before closing the subject of dysmenorrhœa, I feel it incumbent upon me to mention the question of appendicitis in the woman, because of late a large amount of research has been given to this interesting subject of surgical pathology, and from personal experience I would say that when in a female patient there are recurring attacks of pain, especially in the right hypogastric region, accompanied by a rise of temperature, immediately before or during the menses, with irregularity, and more especially delay in menstruation, with abundant leucorrhœa, the attack being accompanied with gastric, intestinal, or nervous disturbances; when all other known causes of dysmenorrhœa can be eliminated, the medical attendant should think of the probability of some form of appendicitis being present.

The genital complication most frequently met with in appendicitis is an inflammatory or a suppurative process of the adnexa, which is usually bilateral, but may involve only the right side. In only a few instances has the appendix been found sufficiently long to reach over into the left side of the pelvis.

In principle, in every woman presenting symptoms of appendicitis a careful and thorough bimanual examination is indicated, while in the virgin an intrarectal, combined with an abdominal examination,

can be practised. On the other hand, in all affections which appear to be distinctly gynecological symptomatically, the possibility of a lesion of the appendix should never be lost sight of, and in operating for diseases of the genital system by the abdominal route, it is prudent, especially if they are of an infectious nature, to search for the appendix and remove it. In every case of appendicectomy, when the adhesions are not too extensive, the surgeon should never fail to examine the condition of the uterus and adnexa.

Metrorrhagia.

Metrorrhagia, like dysmenorrhœa, is simply a symptom, and not an affection *per se*. The so-called essential metrorrhagia does not exist. A hindrance to the free circulation of blood in the uterine vessels, from no matter what cause, will prevent the normal nutritive exchange of the muscle, and more especially of the mucosa, and by this will be produced a change in its structure as well as in its capillary vessels. If a sudden congestion of a reflex nature occurs, producing an increase in pressure, the altered blood-vessels may rupture with the greatest ease, and destroying a diseased and friable mucous membrane, produce a more or less abundant metrorrhagia.

Virginal metritis is a name that has been applied by writers to two very different diseases. The first is an infectious endometritis in every way analogous to that met with in adults.

The second type is termed hemorrhagic metritis. It often makes its first appearance at the time the menstruation is starting in. The menses do not become established regularly, and after one or two periods, often accompanied with great pain, an amenorrhœa occurs. This varies in duration, but usually lasts only a few months. The menses reappear more abundantly, occur nearer and nearer together, and the patient will finally be taken every three weeks, every fortnight, or even flow almost constantly with intervals of repose for three or four days. This form may also make its début after menstruation has been established regularly for several years; but, no matter how this may be, symptoms of anæmia occur very rapidly, and certain authorities have regarded this anæmia as the cause of the menorrhagia.

This pseudometritis undergoes its evolution without fever, and with a very feeble general reaction, which may even be completely wanting. It remains localized, but its duration is variable. Sometimes the metrorrhagic disturbances may rapidly improve, but there are cases reported which have ended in death.

Treatment consists principally in tonics, hydrotherapy, and electricity if indicated. With these means a cure will usually be brought about.

Metritis of the menopause has the same predisposing cause as that met with in virgins, namely, a severe congestion which is a potent factor in the etiology of inflammation of the uterus. As in virginal metritis, we here meet two different forms, the one a chronic metritis, which may have commenced during the genital period of the woman, making its appearance symptomatically only at the change of life; the other, often called hemorrhagic metritis, would be more properly termed metrorrhagia of the menopause.

We are here dealing with a form of metrorrhagia which presents all the characteristics met with in the virginal type. The hemorrhage is, in the first place, of short duration, occurring at certain intervals, which become nearer and nearer together. Changes in the general health take place, and an anæmia, which may reach a very marked degree, is present. The patient will also complain of palpitation, vertigo, sensation of fulness in the head, and hot flushes.

The treatment of metrorrhagia occurring during the menopause must be based on its pathogenesis.

Metrorrhagia symptomatic of carcinoma of the uterus does not occur, when the malignant neoplasm is seated in the cervix, until ulceration has taken place. The physical signs perceptible at this time are quite sufficient for diagnostic purposes.

In carcinoma of the corpus uteri the question is entirely different because here hemorrhages acquire a very great importance. There is nothing special to note as to the manner in which the loss of blood occurs. In some instances the metrorrhagia is so slight that it hardly attracts the patient's attention, while in others the hemorrhage will occur between the menstrual periods under the influence of coitus, straining, or other causes. In still other instances the first hemorrhages take place some time after the menopause has been established, and are regarded by the patient as occurrences to be expected, an error which has been graven in the mind of women for many centuries with most disastrous results.

Usually the metrorrhagia is very abundant, lasting several days, and the intervals which separate the loss of blood become less and less. The patient's general condition rapidly changes, and she not only becomes anæmic from the loss of blood, but cachectic from the presence of the neoplasm, and it is usually at about this time that the physician is consulted. Later on the hemorrhages are replaced by a bloody and fetid discharge, due to a superficial necrobiotic process taking place in the growth.

Metrorrhagia occurring in fibroma of the uterus, like that occurring in carcinoma of the organ, has been attributed to symptomatic hemorrhagic metritis, but in this case as well it would seem that the lesion had been confounded with the symptom. There is no hemorrhagic

metritis, but there are metrorrhagias symptomatic of fibromyomata. The lesions of the mucosa are very variable and do not correspond to those met with in the true hemorrhagic metritis.

These hemorrhages may occur in any stage of the evolution of the fibroid growth, and are as frequent in the very large neoplasms as in the small nuclei infiltrating the walls of the uterus and hardly perceptible by bimanual palpation. Personal experience would lead me to believe that metrorrhagia is more frequent in the latter. Metrorrhagia is not, however, a constant symptom, and is nearly always wanting in the subserous growths and sometimes in the interstitial variety. The loss of blood does not occur suddenly; there is, in the first place, a slight menorrhagia, which lasts for eight or ten days. Metrorrhagia afterward takes place without any apparent cause, and after a time the patients are continually losing blood.

From this it will be seen that there is a slight difference with the hemorrhage met with in carcinoma of the uterus, which is of shorter duration and does not affect the type of prolonged menorrhagia. It is quite evident that these particularities cannot make the differential diagnosis certain, but if attentively considered they will certainly greatly aid in arriving at a correct conclusion.

As to the pathogenesis of the hemorrhages, it may be said that from the beginning of its development the fibroid tumor exercises an irritation on the uterus, which shows itself by a constant hyperæmia. As the growth slowly increases in size, it produces circulatory disturbances in the musculosa and the mucosa, and under the influence of increased pressure and blood stasis the walls of the smaller vessels undergo a calcareous or fatty degeneration, and thus are placed in excellent conditions for an easy rupture. Extravasations of blood occur which detach the superficial layer of the mucosa, and transform the surface of the tumor into a large sanguineous wound.

Metrorrhagia occurring in lesions of the adnexa has been studied only during recent years. True metrorrhagia is not frequent under these conditions; and it is principally in the form of menstrual disturbances that loss of blood symptomatic of tuboovarian disease is met with. There is oftentimes a period of amenorrhœa, following which the patient is taken with a severe menorrhagia, which may last ten or twelve days. Then this symptom quiets down and the menses recur as abundantly as before, if not more so. These large losses of blood rapidly produce a severe anæmic condition and seriously weaken the patient. Hemorrhage symptomatic of tuboovarian trouble is principally met in oöphorosalpingitis. Pain of a severe character ushers in menstruation, and may continue throughout its duration. Tubal colic may also be observed between the menstrual periods, and is usually due to an endeavor on the part of the tube to empty itself, and it is not infre-

quent to find that after a menstrual period, followed by tubal colic, a large quantity of serous or seropurulent liquid escapes from the uterus, which in all probability is in reality the contents of a tube which have been expelled.

The quite distinct characteristics of these hemorrhages should lead one to suspect a lesion of the adnexa, which will be demonstrated by a bimanual palpation. The diseases susceptible of provoking menstrual disturbances are usually solid tumors, and rarely ovarian cystomata, but ovariosalpingitis is by far the most frequent cause. Czempin admits that para- or perimetritic exudates may also give rise to metrorrhagia, and what proves that in these cases we are dealing with a metrorrhagia and not with hemorrhagic metritis is that microscopical examination of the uterine mucosa shows that frequently this membrane is normal, and that the lesions of glandular or interstitial metritis are frequently absent.

Brennecke holds that menstruation is produced by an irritation set up by the ovarian cells on the nervous elements of the ovarian parenchyma. If this development becomes less in intensity, or if the pathological phenomena are such as to oppose rupture of the follicles, the congestion of the uterine mucosa does not attain a sufficient degree to produce hemorrhage, but by remaining present it finally provokes a hyperplasia of the cell elements entering into the formation of the mucosa. Now, when a new flux occurs in this tumefied mucous membrane, a hemorrhage is produced which has little tendency to stop.

It is quite possible also that the tuboovarian disease simply produces an irritation of the ovary, and this, added to the physiological irritation caused by the rupture of the follicle, exaggerates the normal reflex and produces hemorrhage.

No matter what the correct theory may be, we are here dealing with a vascular and nervous reflex, and the difficulty of a successful treatment of these hemorrhages by curettage demonstrates the cause as probably being of extra-uterine origin.

Metrorrhagia occurring in acute metritis is frequent, especially when we are dealing with an acute infection of the uterus. But lost in the midst of a number of serious symptoms, this particular one does not appear as a foremost indication of the affection of the uterus.

The symptoms of acute uterine infection are very characteristic, and consist in chills, fever, intense pain, occurring either after a labor or after a gonorrhœal infection of the external genitals. Menstruation becomes very painful, and the loss of blood, which is irregular in its occurrence, is often mixed with an abundant purulent discharge. The pathogenic diagnosis of this metrorrhagia is easy, but if any doubt should exist, a physical examination will reveal the presence of pus

in the uterus, the organ being extremely tender and increased in size, with an increase of the local temperature.

The duration of the metrorrhagia in these cases is not long, and this symptom is met with principally during the acute stage. When the chronic stage of the infection is reached the metrorrhagia stops, probably because the inflammatory embryonal tissue has given place to organized tissue.

Metrorrhagia occurring during chronic metritis is a symptom by no means constant; in some cases it simply amounts to the loss of a few drops of blood, while in others the amount discharged is considerable, often repeated and producing an extreme anæmia. Menorrhagia is frequent in chronic metritis, while metrorrhagia is rare.

In all forms of chronic metritis there is a formation of fungous masses produced by an hypertrophy of parts of the mucous membrane, and these fungous masses may in some cases be almost entirely composed of vessels which give rise to severe hemorrhage.

Decidual endometritis is perhaps the most frequent cause of metrorrhagia during the genital life of woman. Its study has been taken up only of recent years, although the older writers were well aware that retention in totality or of a large portion of the placenta produced serious phenomena, in the first place of a hemorrhagic nature, and later on of an infectious process, but they were unaware that the presence of a simple chorionic villosity within the uterus, so small that it could hardly be detected, was susceptible of producing a severe and prolonged loss of blood. With the advent of the freer use of the curette the pathology of the condition was studied.

A large amount of retained placental tissue is not necessary for the production of a decidual endometritis, and Kustner was the first who showed histologically the presence of placental elements in a case of metritis post abortum. Fritsch, Schroeder, and Martin held that the inflammation extends to the entire mucosa, having as a starting-point tiny islets of retained placental tissue. The pathogenic part played by this débris is quite obscure, but perhaps there may be an infectious element added to this which produces uterine subinvolution and prevents the regression of its cells to the normal type. Perhaps there may be a microbic metritis, but at the present time nothing definite can be stated in regard to this.

Decidual endometritis has as principal symptom metrorrhagia. The hemorrhages make their appearance several days after a miscarriage, and consequently they can easily be attributed to their true cause. But in other cases the patient is unaware that she has had a miscarriage, and unless a careful interrogatory of her recent menstrual history be made, the possibility of a pregnancy will be overlooked.

The progress of the metrorrhagia in decidual endometritis is typ-

ical. When once it has begun it will continue without ceasing. The patient loses more or less blood every day, but there is never a single day when some blood is not lost. By physical examination all that will be found is a soft dilated cervix usually admitting the finger and an enlarged, softened, and painful uterus. It should be borne in mind that these islets of the placental tissue, especially if a placental cotyledon has been retained, may give rise to the production of polypi, which retain the structure of these large decidual cells.

The probable cause of metrorrhagia in decidual endometritis is a reflex congestion of the diseased mucosa, similar to that met with in cases of intrauterine polypi or in the lesions of an epithelioma of the uterine mucosa at the beginning of its development. What seems to prove this is the constant success obtained by curetting. The cause of irritation being thus removed, the hemorrhage stops completely, and decidual endometritis may be considered the form of all others in which curettage is the only treatment, and in which a cure can be surely expected.

Angiomatous metritis usually occurs in subjects over thirty years of age in women who have had children. There is never any history of miscarriage nor a delay in the menses. The patient who has menstruated regularly commences usually by having a severe menorrhagia, lasting about twice as long as the usual menstrual epoch or even more. The menses then become irregular, and may even be absent for several months. Then metrorrhagia appears suddenly and without any appreciable cause. It is very considerable in amount, consisting of bright red blood mixed with clots if the patient remains quiet. The loss of blood may continue for a considerable length of time, often for several months, leaving only short intervals of respite.

Generally this affection is treated by curettage, and these phenomena will disappear for one or two months, but after this lapse of time blood is lost in the same amount. Then on account of the absence of gross lesions of the uterus and adnexa the case is usually thought to be one of a small submucous fibroid, and the uterine cavity is dilated and explored and nothing is found. The return of the abundant hemorrhages is not long in deteriorating the patient's health, and the anæmic condition becomes pronounced.

On physical examination the cervix will be found enlarged and often soft when seen in the early stage of the disease, but later on it will be found hard, and in nulliparous patients it will be found conical. The entire uterus is increased in size, and to the feel is hard and resistant, but painless. The adnexa are normal and are free from pain on palpation. Seen through the speculum the cervix is normal in color, but its orifice may be either dilated or narrow according to whether the patient is multiparous or not. The uterine cavity is

considerably increased in size, but if explored by the finger nothing abnormal can be found.

The progress of this affection is steady, the loss of blood has no tendency to diminish, and is only from time to time interrupted by short intervals of repose. In other words, the duration is directly associated with the degree of resistance offered by the patient, but sooner or later, if not radically treated, a fatal termination may be expected.

Pathologically angiomatous metritis consists in the presence of a large number of dilated embryonal vessels in the mucous membrane of the uterus, and the dilatation may be so excessive as to take on the cavernous type.

This may be the only existing lesion, but in most cases it is accompanied by lesions of the muscular parenchyma of the organ, characterized by a process of sclerosis seated around the small arteries, accompanying the formation of embryonal connective tissue in which will be discovered dilated capillaries. At a more advanced period of the disease the sclerotic lesions will have been found to have undergone their usual evolution, the muscular tissue being choked by the connective-tissue vessels having thick walls surrounded by a cuff of fibrous tissue.

As to the treatment, it may be said that curetting and the application of caustics have no control whatsoever over the disease. Likewise castration is contraindicated. Ligation of the uterine arteries has been suggested, but would seem a nonsensical procedure, given the pathological anatomy of this affection.

The only radical way of dealing with angiomatous metritis is by hysterectomy, and this will have to be done to save the patient's life.

INSANITY.

BY

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SINCE the publication of the twelfth volume of this work a new theory of the pathology of insanity has been brought forward which is in many respects antagonistic to the opinions which have hitherto prevailed. It is held that all insanity has its origin in toxic action, in toxins derived from without or generated within the body, that the functional action of the cerebral neurones is regulated by the purity of the nutritional supply, and that for every deviation from the healthy state some toxin must be found.

Dr. Ford Robertson, the principal exponent of the toxin theory, read a paper on the subject at the last meeting of the British Medical Association, which is published in the *British Medical Journal*, October 26th, 1901. He states that, in his opinion, in by far the larger proportion of cases the primary etiological factor in the pathogenesis of insanity is toxic action, and that even when depression from some external calamity passes into mental disease, a condition of autointoxication has been produced by the excessive functional reaction, or there has been already established a toxic condition, which is called into action by the sensory stimulus. He attributes little importance to inherited predisposition to insanity, which may be due to modifications caused by toxic action during intrauterine or early extrauterine life, or to inherent defects of cerebral organization, or to differences which individuals exhibit in the reactive qualities of their nerve cells to various forms of toxic action.

According to Dr. Robertson, the various toxic conditions that may cause insanity may result from (1) exogenous toxic agents, (2) infections, and (3) autointoxication and autoinfection. Exogenous agents are such as alcohol, opium, arsenic, lead, and bad maize. These may act primarily on the nutrition of the nerve cells, or may give rise to secondary toxæmias in the gastrointestinal tract and chronic bacterial intoxication. Infections may be caused by syphilis, influenza, enteric fever, tuberculosis, malaria, and diplococcus and streptococcus in-

fections. These may be primary or may lead to the development of secondary toxæmias.

Autointoxication and autoinfection are so closely connected with each other, says Dr. Robertson, that they can hardly be considered apart. Such toxic action may arise at any of the surfaces of the body that normally lodge bacteria, such as the gastrointestinal tract, the larger respiratory passages, and the skin. Autointoxication may further arise from disorder of the functional action of any of the organs and tissues of the body. He wishes, however, specially to insist upon the paramount importance of the gastrointestinal tract in this connection. Its normal functional activity is dependent on a very large number of extremely complex arrangements for the conversion of food materials into nutritive substances, and also upon a series of defensive arrangements against bacteria. The alimentary tract contains a large variety of microorganisms, which would there find every encouragement to their multiplication were it not for certain defensive arrangements by which they are held in check. Where there are extremely complex physiological arrangements, such as those in the alimentary tract, there is the possibility of a great variety of pathological derangements. One of the most important of the tasks lying before the bacteriologist is the investigation of the gastrointestinal flora in health and disease. He believes that various forms of toxæmia of gastrointestinal origin are the chief factors in the pathogenesis of a large array of acute and chronic diseases, cases of senile insanity, general paralysis, locomotor ataxia, chronic alcoholic insanity, dementia præcox, idiopathic epilepsy, and most cases of acute and chronic mania and melancholia, and chronic Bright's disease. He says further that, in his opinion, the large majority of cases of insanity are not primarily diseases of the brain at all, but are dependent on the action of toxins derived from elsewhere, which affect the functional activity of the cortical nerve cells by disordering their metabolism, and often permanently damaging or even destroying many of them. The common view that the "mental disease" is the primary condition is in general founded upon an erroneous conception of what is taking place.

In this review of the pathogenesis of insanity the *quality* of the blood alone is taken into account. Nothing whatever is said of the *quantity* which is circulating in the brain; even anæmia is considered to be associated with toxæmia, and there is no reference to the increase or decrease of the blood supply and pressure caused by mental excitation. Yet that mental stimuli influence this supply is manifest to all observers even from such a simple phenomenon as blushing. In every-day life an unusual event—it may be pleasurable or it may be painful—keeps a man awake by increasing the circulation and producing a hyperæmia of the superior surface of the brain, thus prevent-

ing sleep. If this occurs, not once, but frequently, the balance of the cerebral circulation and the vasomotor control is upset, and chemical changes take place, as well as changes in the vessels and cells, but the origin of all this is psychical fatigue and overstrain, not toxins generated in the gastrointestinal canal. It is a fact beyond dispute that long-continued worry or anxiety produces insanity, and produces it by giving rise to morbid physical conditions. Mental shock or fright may even bring about the rupture of a vessel and apoplectic clot. The gastrointestinal system is one of the earliest and least organized of the human body, the brain and nervous system are the latest and most highly specialized of all, a system prone to disturbance, not only from within, but from without, influenced by surroundings of every kind and affecting the other functions of the body in no small degree. The question arises, Does gastrointestinal disturbance cause brain trouble, or does it owe its origin to the brain? If, as is stated, all insanity is due to toxæmia, and chiefly to autotoxæmia of gastrointestinal origin, why do any escape? A number of people may live under identically the same conditions, eating the same food and drinking the same drink, yet one or two may become insane. Why? Why should these be afflicted, not with the ordinary phenomena of indigestion—sickness, jaundice, colic, or diarrhœa, but with the affection of the brain we call insanity? It is clear that something else must be looked for here, and the explanation of insanity is merely put a stage further forward.

That certain toxins, as syphilis and alcohol, do in some cases cause insanity is an unquestioned fact, and the belief that syphilis is the origin of general paralysis to a large extent is now generally held; but even here the advocates of the toxæmic theory assert that gastrointestinal disturbance is at the root of every case, and that pathological alterations in the alimentary tract are the basis of the disease. Dr. Ford Robertson speaks of the morbid appearances found in the gastrointestinal canal of general paralytics. On the other hand, Dr. Hubert Bristowe found granular disease of the kidney in a large percentage of general paralytics; of seventy-five cases only nine were apparently free from renal disease. It is to be remembered, however, that post-mortem appearances in this form of insanity are those found in patients who have died after a chronic degeneration which has existed for some time and has invaded the whole body. Post-mortem examination of patients who have died at the very commencement of the malady is rare, and seldom occurs in our large public asylums. In the same way the morbid appearances found in those who die of chronic alcoholism are due to a long-continued poisoning of the cerebral structures which has extended to the greater portion of the other structures of the body.

According to this theory, intestinal bacteria are the origin of insanity in as widely differing conditions as general paralysis and acute delirious mania. But we are not told what the specific flora are which generate the one or the other of these insanities. It is clear that the onset of the various forms of insanity is different and depends on different causes. In some it is rapid, the insanity being acute, of short duration, and terminating quickly in death or recovery. Other patients drift into insanity from a state of eccentricity which has been noticed for years. Is there gastrointestinal disturbance in both these varieties? In many there is a marked mental cause—domestic trouble, losses, or worry. Is this to be totally disregarded? Why do patients recover in asylums? They get no special treatment for the intestinal trouble, and we do not read that any is advocated, yet many recover without medical treatment of any kind merely by rest and change of surroundings, as we promised that they would. And, after all, the people who become insane are but a small proportion of the entire population; so that we are driven back to the old question, Why do these become insane and why do these in particular breed toxins in their gastrointestinal canal which caused insanity in the brain? It is difficult to see how the toxin theory can be applied to the large class of patients whose malady is nowadays called "paranoia," and is characterized by one or more delusions, without any acute symptoms of excitement or depression. These "partially insane" people may have the same delusion for years, their bodily health remaining perfectly good. Still more difficult is it to apply the theory to the patients suffering from "folie circulaire," who are sometimes in a state of wild and excited mania and sometimes in the depth of melancholia. Are we to suppose that they breed a special toxin for each of the two conditions? Such a supposition is hardly to be entertained.

DISEASES OF THE SPINAL CORD.

BY

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Injuries of the Spinal Cord.

THE most extensive and accurate description of traumatic lesions of the vertebral columns which are frequently productive of injuries of the spinal cord has in recent years been given by Kocher. These lesions may be produced directly, as the result of force at the site of the lesions, or indirectly.

Excluding puncture and shot injuries, he gives the following table:

A. Partial injuries of the vertebral column. 1. Contusions and distortions of the vertebræ, which also include isolated lesions of the intervertebral cartilages. 2. Isolated fractures of the arches and spines of the vertebræ. 3. Isolated luxations of the lateral articulations. 4. Isolated fractures of the vertebral bodies: generally occurring in the form of compression-fractures.

B. Total luxations and total luxation-fractures of the vertebræ. 5. Luxation-compression-fractures: here the luxation is constantly present in only one or both lateral articulations; the bodies show a pure compression-fracture. This injury is regarded by Kocher as intermediate between A and B, since a total luxation is not present. 6. Total luxation of a vertebra with luxation of the lateral articulations and a displacement of the vertebra into the territory of the intervertebral cartilages. Pure cases show no fracture. Between the atlas and the axis there is constantly present in pure cases a separation of the union between the anterior arch of the atlas and the odontoid process of the axis. 7. Total luxation-fractures. Luxation of the lateral articulation and fracture of the body of the vertebra. Displacements of the lateral articulations, as of the broken portions of the vertebral bodies. The fractures of the vertebral bodies here are generally oblique. Seldom is a pure compression-fracture present. Often both forms are combined. These injuries, called fractural dislocations by

English authors, are among the severe injuries of the vertebral column, and are by far the most frequent.

Pure luxations are produced by flexion of the head upon the chest in falling upon the head. If thereby the head is abducted to one side, a unilateral luxation of the opposite side is produced. Luxations are also perhaps infrequently produced by simple, sudden powerful muscular contraction; for example, of the sterno-cleido-mastoid. Pure bilateral luxations are seldom seen.

Pure fractures of the bodies of the vertebræ are always produced by a force which originates above or below and operates in the direction of the axis of the vertebral column. In falls upon the head the superior dorsal vertebræ are fractured; in falls upon the feet or buttocks the lower dorsal or lumbar vertebræ. Simple fracture of the body of the vertebra corresponds to the isolated fracture of the odontoid process of the axis. The compression of the vertebral body is a preliminary stage of this compression-fracture.

The severe injuries of the vertebral column are naturally produced by the most powerful, direct or indirect force. Marked bending of the vertebral column leads to total luxation and total luxation-fracture; blows upon the vertebral column from above or below lead to compression-fracture.

Ruptures of the intervertebral cartilages, when one is lying, make no trouble; but, when one stands, the case is different. Here the spine, overlying the lesion, can be dislocated forward the same as in fractures of the body of the vertebra. In distortions the deformity of the vertebral column, which usually occurs in the middle cervical region, is similar to that seen in luxations; the head is inclined to the side of the luxation and away from the distortion. The head is held stiff. The pain in distortion is often worse than in luxation, since in the latter the ligaments are torn, but in distortion only stretched. In distortions the deformity can easily be reduced, although this may produce pain. This is naturally not the case in luxations. In pure luxations there is almost always a forward unilateral luxation of the superior vertebra. Posteriorly there is a luxation of the head upon the atlas. In posterior and anterior luxations of the atlas, the odontoid process is generally fractured.

In compression-fractures a kyphosis of the vertebral column is present above the fracture. The spine of the fractured vertebra is displaced anteriorly. A depression is present between it and the spine of the next vertebra. In the recumbent position there is little pain, but on standing marked pain is present; girdle pains are frequent. Not infrequently the sternum is fractured.

In total luxation-oblique-fractures the fracture always passes from above and posteriorly downward and forward. When only one ver-

tebra is fractured, the vertebra superior to the fracture is dislocated forward, luxated in its lower lateral articulations, and has attached to it the fractured portion of the lower vertebra, dislocated anteriorly and downward. If two vertebræ are fractured, in which case the fractured portion of the superior is naturally larger than that of the inferior, both fractured portions united by the intervertebral cartilage are dislocated forward and downward. Oblique fractures from one side to the other are seldom seen. In the worst cases of total luxation-fractures the compression and oblique fractures are so combined that between two obliquely broken vertebral bodies a third is compressed so that the superior luxated body rests immediately upon the second. The total luxation is almost always anterior. The strong longitudinal ligaments are almost never ruptured. In partial spinal injuries lesions of the spinal cord and nerve roots are seldom seen, and, when present, under appropriate treatment usually quickly improve. In distortion the symptoms may be entirely limited to those produced by injury of the nerve roots. Here there may arise, corresponding to the height of the lesion, pains, paralyses, and anæsthesias, unilateral or bilateral, in the territory supplied by the brachial plexus; and if cord lesions are present spastic symptoms in the lower extremities and not infrequently disturbances of the bladder and large intestine. In pure luxations of the superior cervical vertebræ cord symptoms may be entirely absent. If they are present, both they and the root symptoms are similarly grouped, as in distortions. The cord symptoms are naturally more severe. In simple compression-fractures, corresponding to their location in the lower portion of the vertebral column, paralysis and disturbances of the tendon reflexes are frequently observed. Almost always in such injuries of the spinal column the cord is only partially injured, and the anæsthesias and paralyses involve only the territory of the lesion. In total luxations and luxation-fractures, on the other hand, there is almost always present a complete destruction of the cord through crushing or rupture. Crushing occurs between the arches of the luxated and the next succeeding vertebra, and hence corresponds to the site of the injury. Rupture of the cord, however, takes place as the result of overstretching, and hence the location of the tear may be quite far removed from the site of the luxation. In some cases of severe contusions of the cord the lesion may, as the direct result of the injury or from secondary softening, extend farther above the spinal injury, which, from the objective symptoms alone, would be regarded as higher than was actually the case.

Pathological Anatomy.—The minute histological changes produced in the substance of the spinal cord by traumatism are swelling, fragmentation, and destruction of the cord sheath; swelling, segmentation,

and spiral distortion of the axis cylinder; hyaline masses are subsequently found in the widened and œdematous meshes of the glia; later these spaces are empty; the tissue appears streaked (Schmauss). The torn nerve ends have a tendency to grow again in the direction of their long axis; they press into the nerve tissue, but they seldom reach their corresponding nerve ends or the ganglion cells to which they belong, so that they can again become intact. Animal experimentation has recently shown that such young nerve fibres, running in the adventitia of the vessels, reach by a very complicated route the surface of the cord, and thence reach the motor ganglion cells, to which they belong, lying below the lesion. At present it is not possible to deny that a spinal-cord lesion may heal and function be restored, but it is certain that such healing processes have very narrow limits.

Hemorrhages into the central canal may be present, for example, in lesions of the conus, and the blood may rise to the cervical region and produce extensive symptoms, which, however, later subside.

Symptomatology.—In lesions of the upper cervical region unilateral or bilateral pupil and lid contractions may be observed. The dilator fibres arise in the medulla oblongata, pass through the entire cervical portion of the cord, and chiefly emerge at the first dorsal vertebra.

Our knowledge with respect to the motor and sensory relations of the segments of the spinal cord, especially the lumbar segment, has in recent years very much increased and become much more accurate than was formerly the case. Below is a table which shows much alteration from that given in Vol. XI., p. 577:

LOCALIZATION OF THE FUNCTIONS OF THE SEGMENTS OF THE SPINAL CORD.

Segment.	Muscles.	Sensory cutaneous distribution.	Reflex.
1st cervical.	M. rectus capitis posterior minor. M. rectus capitis posterior major. M. obliquus capitis superior. M. semispinalis capitis. M. spinalis capitis (pars cranialis). M. rectus capitis anterior. M. longus capitis. M. rectus capitis lateralis. M. geniohyoideus. M. omohyoideus. M. sternohyoideus. M. thyreohyoideus. M. sternothyreoideus. A branch to the m. intertransversarius posterior cervicalis.		

LOCALIZATION OF THE FUNCTIONS OF THE SEGMENTS OF THE SPINAL CORD.—*Continued.*

Segment.	Muscles.	Sensory cutaneous distribution.	Reflex.
2d cervical.	M. rectus capitis posterior major. M. obliquus capitis inferior. M. semispinalis capitis. M. spinalis capitis (pars cranialis). M. longus atlantis. M. longus colli. M. longus capitis. M. geniohyoideus. M. omohyoideus. M. sternohyoideus. M. thyreohyoideus. M. sternothyreoideus. M. splenius capitis et cervicis. M. sterno c l e i d o m a s-toideus. M. trapezius. Prolongations of the m. longissimus and intertransversarii.	Skin of the occiput to the crown of the head; to the sides of the head anteriorly to the anterior limit of the ear; to the posterior inferior portion of the lower jaw from before backward to the second rib; posteriorly to the spine of the scapula (according to Wichmann the middle lower portion of this dorsal territory is supplied by the dorsal branches of the 5th, 6th, and 7th cervical nerves).	Reflexes of the extensors of the arm and forearm.
3d cervical.	M. longus atlantis. M. longus colli. M. longus capitis. M. diaphragma. M. scalenus medius. M. geniohyoideus. M. omohyoideus. M. sternohyoideus. M. sternothyreoideus. M. splenius capitis et cervicis. M. stern o c l e i d o m a s-toideus. M. trapezius. M. levator scapulæ.		
4th cervical.	M. longus atlantis. M. longus colli. M. longus capitis. M. diaphragma. M. scalenus anterior. M. scalenus medius. M. sternothyreoideus. M. splenius capitis et cervicis. M. trapezius. M. levator scapulæ. M. rhomboidei. M. supra- et infraspinatus M. deltoideus. M. biceps et coracobrachialis. M. supinator longus.		
5th cervical.	M. levator scapulæ.*	External surface of the	Scapular reflex.

* In addition the muscles covering the entire vertebral column at the corresponding height.

LOCALIZATION OF THE FUNCTIONS OF THE SEGMENTS OF THE SPINAL CORD.—*Continued.*

Segment.	Muscles.	Sensory cutaneous distribution.	Reflex.
5th cervical.	M. teres minor. M. diaphragma. M. rhomboidei. M. deltoideus. M. biceps et coracobrachialis. M. brachialis internus. M. supinator longus et brevis. M. pectoralis (pars clavicularis). Perhaps extensors of the hand. M. serratus anticus major M. splenius.	shoulder, arm, and forearm.	From the 5th cervical to the 1st dorsal root tendon reflexes of the muscles thereby supplied.
6th cervical.	M. deltoideus. M. teres major et minor. M. biceps et brachialis internus. M. supinator longus et brevis. M. subscapularis.	External surface of the forearm on the flexor and extensor surfaces.	
	M. pronator quadratus et teres extensors and flexors of the hand. Serratus anticus major. Perhaps long extensors of the fingers. M. splenius. M. scaleni. M. triceps.	Radial territory of the hand and fingers.	
7th cervical.	Pronators of the hand. M. subscapularis. M. teres major. Extensors and flexors of the hand. M. triceps. Pectoralis (pars costalis). Latissimus dorsi. Long extensors and flexors of the fingers. M. splenius. M. scaleni. Small muscles of the hand (interossei and lumbricales [?]).	Middle portion of the forearm on the flexor and extensor surfaces. Radial and median territory of the hand and fingers.	Palmar reflex. Blows upon the vola manus produce closing of the fingers.
8th cervical.	Flexor carpi ulnaris. Long extensors and flexors of the hand. Interossei and lumbricales. Scaleni.	Ulnar side of the hand, of the arm and forearm on the flexor and extensor surfaces; the same surface of the arm is also supplied by the second dorsalis.	
1st dorsal.	Long flexors of the fingers Interossei and lumbricales. Ball of the thumb and little finger. Scaleni. In the 8th cervical and		

LOCALIZATION OF THE FUNCTIONS OF THE SEGMENTS OF THE SPINAL CORD.—*Continued.*

Segment.	Muscles.	Sensory cutaneous distribution.	Reflex.
	1st dorsal roots fibres are given off to the dilator pupillæ.		
Dorsales 2 to 12 and 1st lumbar.	The corresponding muscles of the vertebral column. M. serratus posterior superior 1 to 4. M. serratus posterior inferior 9 to 12. M. intercostales interni 2 to 11. M. intercostales externi 2 to 11. M. levator costales breves 2 to 11. M. infracostales 2 to 4 and 7 to 9. M. levator costales longi 8 to 10. M. transversus thoracis 3 to 6. M. transversus abdominis VII., 1 to 1. M. obliquus abdominis internus VIII., 1 to 1. M. obliquus abdominis externus IV., 12. M. rectus abdominis V., 12. M. pyramidalis dorsalis 12, 1 to 1.	Skin of the breast, back, and abdomen, from the lower limit of the cervical region above nearly to the inguinal folds below. Skin of the superior gluteal region. The 6th root extends anteriorly to the middle of the epigastrium, the 8th and 9th supply the abdomen (4th dorsal root the nipple, 6th the superior epigastrium, 10th the navel). The boundary lines of the above-described territories run horizontal to the buttocks; also to the thorax over several intercostal spaces.	Epigastric reflex. 4th to 7th dorsal roots. Abdominal reflex 1st to 11th dorsal roots.
	Lumbar Plexus.		
Lumbalis 1.*	Abdominal muscles. Iliopsoas. Sartorius. Cremaster.	Skin of the inguinal region, of the superior, anterior external portion of the thigh. Skin of the mons veneris, of the anterior surface of the scrotum. To the testicle, semen passages and tunica dartos (?).	Patellar reflex. 2d to 4th lumbar.
Lumbalis 2.*	Iliopsoas. Sartorius. Quadriceps femoris. Cremaster.	External and anterior surface of the hip to the lower third of the thigh.	
Lumbalis 3.	M. iliopsoas. M. sartorius. M. quadriceps femoris. M. adductores femoris.	Anterior surface of the hip in common with the 2d lumbar, and the inner side of the leg to the inner malleolus.	
Lumbalis 4.	M. quadriceps femoris. M. adductores femoris. Tibialis anticus (extensor digitorum communis; extensor hallucis).	Lower portion of the inner and anterior portion of the hip. Inner side of the leg, inner border of the foot and great toe.	Gluteal reflex. 4th and 5th lumbar.

* Possibly the 1st and 2d lumbar segments contain no motor fibres; then the here designated muscles receive their supply from the 3d lumbar segment.

LOCALIZATION OF THE FUNCTIONS OF THE SEGMENTS OF THE SPINAL CORD.—*Continued.*

Segment.	Muscles.	Sensory cutaneous distribution.	Reflex.
	Sacral Plexus.		
Lumbalis 5.	Dorsal flexors of the feet (tibialis anticus). Extensor digitorum communis. Extensor hallucis. M. peronei. Flexors of the knee. Abductors of the hip. External rotators of the hip. Extensors of the hip and adductors (?). Plantar flexors of the hip and long flexor tendon.	Anterior, external surface of the leg, external and dorsal surface of the foot with the exception of the great toe, inner surface of the planta pedis (with the 1st sacral) (according to Thoburn also to the posterior external portion of the hip and thigh [?]).	
1st sacral.	M. peronei. Plantar flexors of the foot Long flexor tendon of the great toe. Flexors of the knee. Abductors and external rotators of the hip.	External and middle portions of the sole, instep, part of the dorsal surface of the foot and great toe. External and posterior surface of the calf.	Plantar reflex.
2d sacral.	Extensors of the hip. External rotators of the hip. Small foot muscles. Spec. interossei and flexor digitorum brevis.	External border of the foot, external surface of the sole, middle portion of the posterior surface of the thigh and leg.	Tendo Achillis (according to Zeihers, 1st sacral).
3d to 5th sacral.	Muscles of the perineum and striped muscles of the urethra, large intestine, and organs of generation.	3d sacral: Skin over the os sacrum, inner side of the most superior portion of the thigh. 4th and 5th sacral: Perineum, anus, posterior surface of the penis and anterior surface, with the exception of the root of the penis. Posterior surface of the scrotum (in women the posterior portion of the labia majora).	Centre of erection 2d and 3d sacral; ejaculation, 3d sacral; detrusor and sphincter vesicæ 3d, 4th, and 5th sacral; sphincter ani 3d and 4th sacral. The centre for the sphincter ani is always below the centres for the detrusor and sphincter vesicæ.

Disturbances of the functions of the bladder and large intestine are very manifold in their manifestations in injuries of the spinal cord; not, indeed, in accordance with the extent of the injury or its specific location, as was formerly supposed. In partial lesions of any location bladder disturbances vary widely. In total divisions of the spinal cord in any location above the reflex bladder centre, situated in the lower sacral region, the bladder disturbances are severe. Here

generally at first there is present retention, which may continue for a week. Later, according to Müller, catarrh of the bladder may supervene and incontinence set in, either ischuria paradoxa, or frequent reflex urination without the knowledge of the patient. In these cases the sphincter vesicæ internus is still intact. But later, in total divisions of the spinal cord of whatever location, paralysis of the internal sphincter occurs. Even here in the recumbent position a small quantity of the urine may be retained through the elasticity of the sphincter, but only a small quantity, so that there is always dribbling or urination only in small quantities.

Formerly it was thought that paralysis of the sphincter internus and constant passive dribbling, with a nearly empty bladder, occurred only when the lower sacral region and the bladder centre were directly destroyed. According to Müller, however, in such cases we have at first a retention of the urine, and later a reflex emptying of the bladder. Müller thinks that the reflex evacuation of the bladder is not brought about through the spinal cord, but by a reflex in the sympathetic system, which, however, may be inhibited by a high or low complete division of the cord.

The sphincter ani externus is striped voluntary muscle whose centre is in the lower sacral region. In high total divisions of the spinal cord a voluntary contraction of this muscle is naturally impossible. It, however, contracts reflexly, and the anal reflex in such lesions is very frequent. In lesions of the conus it is paralyzed, and the anal reflex is wanting. But since in these cases the sphincter ani internus still contracts reflexly, the evacuation is prevented or restrained a long time by the voluntary contraction of the sphinter ani externus. Thus, in lesions of the conus the fæces are not passed continuously, but are retained until, by an overfilling of the large intestine, the sympathetic reflex becomes operative.

I will also add that, according to Müller, the production of an erection and the emission of semen from the "semen bladder" in the prostatic portion of the urethra is exclusively a sympathetic reflex. Only the ejaculation of semen is produced voluntarily by muscles whose centre is in the sacral region.

At present it must be regarded as certain that, in most cases of total high transverse spinal-cord lesions, the tendon reflexes of the lower extremity are lost. Nevertheless, the cases of Kausch and F. Schultz—in which the upper dorsal region was surgically divided—show that this is not a universal law. In this case the reflexes at first were lost, later returned; were for a time increased, and then became weak, and gradually vanished a few days before death. Why in most cases the reflexes are permanently absent has not been definitely settled.

In unilateral lesions of the spinal cord in most cases mere sensi-

bility to pain and temperature is lost on the opposite side. Researches in human pathology show that the old idea of Brown-Séquard of the crossing of the pain and temperature fibres, at least, is correct. These fibres cross in the gray substance close to their exit from the same and thus pass into the opposite anterior nerve (Oppenheim).

Prognosis and Treatment.—The prognosis of total luxations and total luxation-fractures, with severe injury of the cord, is almost always very grave. In a few cases, in which the injury is not located too high, life may be prolonged; but permanent paralysis results. In partial spinal injuries the cord and root symptoms may entirely subside, except as they can be referred to hemorrhages in the spinal meninges, œdema, and ascending hemorrhage in the central canal. Only in these cases is therapy at all possible and effective.

Luxations should be reduced; compression-fractures and distortions made immobile for a long period. Caries, according to Kocher, frequently follows the former and a rarefying ostitis the latter.

Spinal Caries.

Pathological Anatomy.—A carious abscess arising from a vertebral body may at first remain under the periosteum and the ligamentum longitudinale posticum. Later this ligament may be weakened and the spinal cord compressed. In these cases with the evacuation of the abscess the prognosis of the cord lesions becomes very favorable.

According to Schmauss, vertebral caries is most frequently seen in the lumbar portion, next in the dorsal portion, and least frequently in the cervical portion. But caries of the dorsal portion most frequently involves the spinal cord (in about eighty per cent. of cases). The infrequent involvement of the lumbar portion of the cord is to be accounted for by the fact that in spinal caries of the lumbar vertebræ the third lumbar is most frequently the seat of the disease, while the spinal cord terminates at the second lumbar.

Pachymeningitis externa tuberculosa scarcely ever merely produces pressure, but generally operates by causing compression and thrombosis of the veins of the pia.

Recovery from paralysis after such a long period of compression, that a sclerosis of the cord must have resulted therefrom, may occur. It is probably due to a new formation of the enclosing membrane of the cord and a regeneration of the ganglion cells, after the healing of the bone and epidural lesions. Schmauss believes there is no new formation of the nerve fibres.

Symptomatology.—In spinal caries, producing partial lesions of the superior portions of the cord, there is frequently observed an absence of the patellar reflex and a paralysis of the lower limbs. In some

cases these appearances are to be explained by an anatomical lesion of the peripheral reflex circuit, be it of the roots, of the peripheral nerves, or of the ganglionic cells of the anterior horn (A. Westphal). In such cases naturally the remaining signs of a total division of the spinal cord are absent. Cases of minute tuberculous lesions of the dorsal cord, according to Chehault, are suitable for operation. They are, however, very difficult to diagnose, with respect both to their character and to the location of the lesion.

Diagnosis.—For the frequently difficult differential diagnosis between spinal caries and spinal carcinoma the following new points are especially valuable, according to my own experience and also that of Schlesinger:

In carcinoma there is usually found a round projecting deformity of the spinal column, while in caries such is sharp-pointed. Lateral displacement of the spines is found only in carcinoma (Schlesinger). In addition in carcinoma there are present spontaneous pains in the vertebra, with an absence of tenderness upon pressure upon the spines; also a tenderness upon pressure near such diseased vertebra. In spinal caries of the cervical vertebræ there is often present a hard tumor, discernible both by sight and upon pressure. Here a false diagnosis of osteosarcoma or enchondroma is frequently made. Carcinoma, on the other hand, is not easily confounded therewith. In such cases a disappearance of the tumor makes sure a diagnosis of caries. The presence of abscesses and the occurrence of complete healing are sure signs of caries.

The root or cord symptoms are not sufficient for a differential diagnosis. It can only be said that severe and distinct root symptoms, if they remain isolated for a long time, such as pains, circumscribed muscular atrophies, and herpes zoster, are frequently observed in carcinoma. However, all these symptoms may also be present in caries. In a case which I have observed and which serves as an example of the long isolated existence of root symptoms in spinal carcinoma, I found post mortem a pachymeningitis interna carcinomatosa. Acute compressions of the cord, through a coincident fracture of the diseased vertebræ, are more frequently present in carcinoma than in caries. Even here, however, they are more frequently met with in the cervical portion of the vertebral column.

More difficult still than the differentiation between spinal caries and carcinoma is that between sarcoma and caries. The first point of value is the frequent occurrence of sarcoma in youth and childhood; second, one can often primarily demonstrate the presence of tumors posteriorly in the region of the coccyx, and not infrequently on the spinal column.

Chronic amyloid degeneration of the vertebral column and trunk

articulations (spondylitis rhizomelica) causes, in the form specially described by Bechterew, root symptoms (pains and muscular atrophies), but never cord symptoms.

Prognosis.—According to Fickler, recovery from pressure paralysis of the spinal cord, resulting from caries of the vertebral column, takes place in about fifteen per cent. of cases. It is possible, however, for the severest symptoms to continue a long time.

Treatment.—In two cases I have seen a very favorable influence upon the paralysis as the result of a forcible reduction of the spinal deformity. In the first case, in which sensory and motor paraplegia of the lower extremities was present, both of these symptoms disappeared twenty-four hours after the operation. Here there could have been present only a simple compression or a rapidly disappearing œdema of the spinal cord. The patient has entirely recovered. In the second case the paralysis of the legs slowly disappeared after the operation, but the patient still suffers from abscesses and a tuberculosis of other bones, and recently an amyloid degeneration of the intestines has appeared.

Tumors.

In the classification of spinal tumors, the earlier subdivisions of which may still be retained, among the extradural forms those deserve especial prominence which lie partly outside, partly inside of the vertebral canal. These tumors have, so to speak, an hourglass form, composed of a greater extra- and an intravertebral portion, which are united by a slender portion, which passes through small fractures of the vertebra. Such an arrangement, according to Schlesinger, is found in sarcomas, lipomas, echinococci, and, perhaps, also in enchondromas.

Tumors of the Spinal Column.

The following varieties of tumors may be observed in the vertebral column. According to the frequency of their occurrence they are carcinoma, sarcoma, myxo-, fibro-, and melanosarcoma; furthermore, alveolar sarcoma, exostosis and osteomas, and excessive callus formations; enchondroma, myeloma, and very rarely gummata. Benign tumors of the vertebral column are much less frequently seen than malignant; about one to ten (Schlesinger). Vertebral carcinoma is never primary. The primary seat of the carcinoma varies. The most frequent location is the body of the vertebra. In vertebral carcinoma, associated with fractures of the diseased vertebra, the deformity is generally rounded. Not infrequently the spinal processes are displaced laterally (Schlesinger).

Sarcomas, either primary or secondary, may be present in all possible forms in the vertebral column. Melanosarcoma occurs only secondarily. It most frequently originates in the periosteum; seldom in the marrow of the vertebral bodies. In general direct destruction or compression of the spinal cord is more frequently seen in connection with vertebral carcinoma than with vertebral caries.

Periosteal exostoses are most frequently seen, according to Schlesinger, in the coccyx and lumbar vertebræ; seldom above this location.

Enchondromas are very seldom seen in the vertebral column. When present, they usually arise on the external surface of the vertebra and press through the intervertebral spaces into the canal.

Multiple myelomas of the vertebral column are more frequent. When present, the spinal foramina of a large number of vertebræ are usually riddled by a tumorous mass, which approaches the structure of lymphatic bone tissue. The bones are much softened thereby; the vertebral column becomes kyphotic; frequently, however, these tumors produce a new formation of ivory-like bony masses. The cord in such cases is nearly always injured. Of clinical and diagnostic importance in these cases is the presence of albumose in the urine, fever, and the occurence of similar lesions in other bones.

Echinococcus is only seldom primarily seen in the vertebral bodies, which it destroys. The cord is compressed. As a rule, the primary seat of the lesion is in the neighborhood of the vertebra in the subpleural or subperitoneal space, or in the back muscles. It is observed in every portion of the vertebral column. The cysts may be the size of a walnut or larger.

Gummata are very seldom found in the vertebræ. When present, they most frequently are found in the cervical vertebræ, and, according to Gowers, stand in direct relation with syphilitic pharyngeal ulcers. Spinal syphilis and spinal caries are always very difficult to differentiate from each other.

Symptomatology.—It is often the case that for a long period the symptoms are limited to lesions of the bone, of the roots, or of the cord. Very infrequent is the entirely isolated appearance of cord symptoms without bone and root symptoms. This is possible, however, at least in carcinoma of the dorsal portion of the cord. Of the possible combinations in chronic cases bone and cord symptoms, with the absence of root symptoms, are seldom seen. Permanent or long-continued limitation to bone and root symptoms and the absence of cord symptoms, or to cord and root symptoms and the absence of bone symptoms, are very frequent in spinal carcinoma.

There are not infrequent cases in which all the symptoms are so indefinite that a correct diagnosis is scarcely possible. These cases are sometimes regarded as hysterical in nature.

Objective root symptoms are more frequent in spinal carcinoma than in spinal caries (muscular atrophies and hyperæsthesias of the skin, herpes zoster). Very large tumors of or near the vertebral column are much more frequent in spinal sarcoma than in spinal carcinoma. Frequently also such tumors are pulsating.

The remaining spinal tumors, with the exception of myelomas, whose symptomatology has been given above, are to be differentiated from carcinomas and sarcomas principally by the spinal symptoms. Thus enchondromas, gummata, and frequently echinococci are limited to one vertebra, while in carcinoma and sarcoma a number are involved. Exostoses are also frequently multiple, but they usually involve non-contiguous vertebræ. In exostoses pressure pains are usually absent, and also alterations in the form of the vertebral column are infrequently seen. If root and cord symptoms are present at first, they are similar to those seen in spinal carcinoma and sarcoma.

Diagnosis.—The important differential diagnosis between spinal caries and carcinoma has been considered in the section on "Spinal Caries." The differentiation between intravertebral and vertebral tumors is made more difficult by the fact that in the former disturbances of the nutrition of the bones may give rise to changes in the form of the vertebral column, although the tumor does not come in direct contact with it. Very important is the fact that in the presence of primary carcinoma and sarcoma in other regions of the body a vertebral tumor is more probable than an intervertebral. Schlesinger says that the presence of atheromatous pains in the legs, together with kyphosis and progressive stiffening of the vertebral column, and Kümmel's rarefying ostitis are very significant of the presence of a vertebral tumor.

Therapy.—Primary and secondary spinal sarcomas have been subjected to operation with at least a prolonged favorable result (Kümmel). In one case, reported by this author, in which only a small portion of the sarcoma could be removed, the division of a number of the posterior roots in the region of the tumor was followed by a very good result. In these cases the general condition of the patient, possible metastases in other organs, and the condition of the spinal cord must receive due consideration *pro* and *con.*

Spinal echinococcus is very easily operated upon, but there are so many cysts usually located in non-accessible portions of the vertebral columns that little good is to be obtained from an operation; also in the vertebral column itself echinococci may be very multiple. In operating upon multiple exostoses it must be borne in mind that a re-formation may easily occur in other locations; also hypertrophic callus may easily recur after removal.

Schlesinger has seen favorable results and recovery from the energetic use of arsenic in lymphosarcoma. A permanent maintenance of the horizontal position frequently diminishes the pains (Schlesinger).

Tumors of the Spinal Meninges and of the Cord Itself.

Intramedullary tumors are nearly as frequent as those of the meninges, extra- and intradural (Schlesinger). Extradural tumors are usually metastatic. Extradural tuberculous tumors or gummata, without involvement of the bones, meninges, or cord, are very infrequent. Extradural lipomas are not infrequently of hourglass shape. They lie half extra- and half intradural. Such an arrangement is also frequent in extradural echinococci. These are often multiple. Extradural cysts have never as yet been observed. Intradural may be primary or secondary, but the former are by far the most frequent.

The most important primary tumors are different forms of fibroma and sarcoma, which not infrequently originate in the spinal roots.

Psammomas (sarcoma angiolithique of the French) are also to be included among the sarcomas. They are of very slow growth and have frequently been successfully operated upon.

A very important form of spinal-cord sarcoma is the multiple sarcoma of the meninges. Therapeutically these are of little importance. Generally they are coincidentally present in the brain, and usually, although not always, do not involve the substance of the cord. The roots are but little injured.

Endotheliomas occur on the internal surface of the dura in the form of multiple small tumors. They are also seen as isolated large tumors in the arachnoid tissue. Only one observation is recorded of a cholesteatoma of the pia of the spinal cord. Lipomas are found inside of the spinal meninges, as a rule, in combination with spina bifida, and so are usually found in the lower dorsal and superior lumbar regions. In such cases mixed tumors are frequently found—myofibrolipomas.

Teratomas are found in the lower portion of the vertebral canal. They may not be associated with spina bifida.

Multiple neurofibromas, involving nearly all the spinal roots, have once been observed in association with general peripheral neurofibromas and neurofibromas of the cerebral nerves, some of them being large enough to compress the cord.

Of the secondary tumors of the spinal meninges the following may be mentioned: sarcomas, multiple melanosarcomas, multiple carcinomas, which are very infrequent, and when present are generally also to be found in the brain, and metastatic multiple gliomas of the cord and meninges, which arise from the glioma of the network.

The most frequent are tubercles, which are really not tumors; the

next most frequent are gliomas. Tubercles arise, as a rule, in the gray matter of the anterior or posterior horns. They may be bilateral. Gummata of the spinal cord usually arise in the pia and stand in continuous union with it. A cholesteatoma of the substance of the spinal cord has been once observed. Sarcomas are rare. As has been said, carcinomas and retinal gliomas occur metastatically in the spinal cord.

Occurrence and Etiology.—In general, tumors of the spinal cord and its meninges are of infrequent occurrence. Cerebral tumors are nearly six times as frequent as tumors of the spinal cord. In 35,000 autopsies spinal-cord tumors were found in 330—about 0.3 per cent. Tumors of the vertebræ are, however, not included among this number. Tumors of the vertebræ are more than twice as frequent as intravertebral tumors (Schlesinger). In the same 35,000 autopsies tumors were present in some portion of the body in one-fifth of all the cases (6,540), but in only 2 per cent. were they found in the vertebræ, spinal meninges, or spinal cord. Intravertebral tumors are found at every age. Certain species of tumors show a predilection for certain ages. Other species show little or none. With respect to this matter, I follow entirely the views of Schlesinger. In children under ten years of age the most frequent intramedullary tumors are solitary tubercles, extramedullary (up to five years of age), lipomas (spina bifida), or metastatic gliosarcomas; later diffuse multiple, metastatic sarcomas. From ten to twenty years of age intramedullary tubercles and gliomas predominate. At this age primary intramedullary sarcomas are very infrequent. Extramedullary multiple sarcomas are especially frequent in women, and echinococci in men. Multiple neuromas also show a preference for adult age.

The same holds true for twenty to forty years of age. From the fortieth to the sixtieth years intramedullary gummas are more frequent than tubercles. Extramedullary at this age of especial frequence are slow-growing, practically benign, isolated tumors (these are favorable for operation)—sarcomas, psammomas, fibromas, echinococci, and cysts. Metastatic and diffuse tumors are infrequent. Over sixty years of age extramedullary psammomas and fibromas are the most frequent—the former in women and the latter in men. In general the forms which give the more favorable prognosis increase in frequency with the age of the patient.

A very marked difference in the frequency of tumors of the meninges between the sexes does not exist. According to Schlesinger, however, the intramedullary forms are more frequent in men, as is also the case with all intravertebral tumors.

According to Schlesinger, of all intervertebral tumors, intramedullary tubercles are the most frequent, then follow gliomas; sarcomas

come third. These are, however, much more frequent in the meninges. All other forms are very infrequent.

The various forms of tumors are found with varying frequency in different portions of the vertebral column. In the cervical portion are found intramedullary tubercles, gliomas, and gummas; in the meninges, sarcomas, fibromas, psammomas, and myxomas; in the dorsal portion tumors are especially frequent in the meninges, extra- and intradural; then sarcomas, myxomas, and echinococci. Here intramedullary tumors are rare. Such are, however, frequently found in the sacral portion, especially tubercles and gummas. Extradural in this portion of the cord, sarcomas, psammomas, echinococci, and lipomas are found. Rare forms of tumors are especially frequent in the cauda equina (cylindromas, myolipomas, lymphangiomas, angiomas). With respect to the etiology of tumors of the spinal cord, we know very little. The etiology of the infectious granulomas (tubercles and gummata), parasitic and metastatic tumors is relatively clear; but usually the reason why the primary or metastatic tumors affect the cord in one case and the meninges in another is not discernible.

Tubercles and gummas frequently develop in the tissues of tuberculous and syphilitic individuals when such tissues are exposed to traumatism. The same with respect to echinococcus (Schlesinger).

Of the primary tumors of the spinal cord glioma is closely related to traumatism, particularly when accompanied by the formation of a depression. In these tumors heredity plays a certain part, or it may be that gliomas, so small as to produce no symptoms, have been present from the earliest years. It is doubtful whether with an hereditary predisposition a progressive syringomyelitis can result from a traumatic hæmatomyelitis with the formation of a cavity (Schlesinger). Practically the most important tumors arising in this manner are malignant tumors of the vertebræ, carcinoma, and, perhaps more frequently, sarcoma.

It is interesting to note that not infrequently symptoms of a tumor of the spinal cord develop after infectious diseases and severe labors with marked hemorrhages and puerperal infection. An hereditary predisposition appears to be present in many cases of diffuse sarcoma of the meninges.

Symptomatology.—Among the early signs of beginning compression of the spinal cord are spasmodic movements of the limbs, which may appear suddenly or gradually and eventuate in a flexion of the hip. They may last throughout the whole course of the disease, even if total motor and sensory paraplegia is present. In some cases these spasmodic movements are accompanied by severe neuralgic pains. Here the movements are reflex, caused by an irritation of the sensory

nerve roots. In other cases only the powerful contractions are painful. If the contractions are present with total motor and sensory paralysis of the legs, they may owe their origin to cutaneous reflexes of the paralyzed limbs, which under these conditions are often greatly increased and produced by contact, for example, with bedclothes.

In tumors located centrally in the gray substance, especially tubercles, the pains may form a very insignificant part of the clinical picture. If the tumor is located in the anterior horn, rapidly progressing spinal muscular atrophies are a prominent feature, since these tumors quickly extend in the long axis of the cord. Moreover, the clinical picture may more resemble that of a subacute or chronic myelitis or syringomyelitis. Here nearly always the symptoms are bilateral from the beginning. Extradural tumors, which often surround the long axis of the cord as a cylindrical covering, may give rise to very extensive root symptoms. Under certain conditions, however, the roots may not be affected.

Symptoms relating to the bladder and large intestine are similar to those in injuries of the spinal cord, only they differ somewhat in establishment and progression.

In complete paraplegia, caused by compression tumors, I have usually seen absence of the patellar reflex, if the site of the compression is high. Occasionally this symptom appears very late in the course of the disease. Perspiration is also absent in the motor and sensory paralyzed parts (Bruns and Schlesinger).

Course.—The pains accompanying very small intradural tumors may extend over a long period, and often in single attacks change their location (Schlesinger and F. Schultze). Root pains may continue many years or cease for long periods. Of intradural tumors, isolated sarcoma, fibroma, and psammoma are of the longest duration. Here durations of two, four, eight, and fourteen years are observed; the average duration is about three years. The duration of multiple sarcomas, neurofibromas, and parasitic cysts is shorter. Of the extradural tumors, lipoma shows the longest duration. Of intramedullary tumors, tubercles and gummas are the most rapid (nine and seven and one-half months). Sarcomas and gliomas run a course of two years or more.

Diagnosis.—Recent especially favorable operation results show (Allen Starr, Oppenheim, and others) that the general diagnosis, as well as the location of site of the tumors, may be definitely determined if, in addition to the objective root symptoms, primary cord symptoms are present, and, indeed, previous to the appearance of the cord symptoms.

If a "pain zone" lies above an anæsthetic zone, which corresponds in extent to only one segment, then, since, according to Sherrington,

in total anæsthesia of the fifth dorsal segment the fourth must also be destroyed, can the pains in the fourth segment only depend upon an involvement of the third vertebra? If, however, the pains in such a case are also present in the territory of the third or second segments, it is not necessary to conceive that in such an extensive "pain zone" the first dorsal vertebra is involved, since the pains may all be produced by the involvement of the third vertebra, which extends to the fourth vertebra below and the second above. In this case one must also ascribe the high location of the symptoms to the involvement of a root which passes out from the main root below the site of the lesion, and in this case the pains could extend to that height of the vertebral column at which the tumor is located. It is to be noted that Schlesinger has often observed pains in a territory far removed from that which corresponds to the involved portion of the cord. Such are, perhaps, produced by transmissions through the cord. In such cases these pains are of no value for the diagnosis of the site of the cord lesion.

Conclusions with respect to the type of the tumor can be drawn only when its location is known—intramedullary, intra- or extradural.

Prognosis.—The earlier extremely unfavorable prognosis of spinal-cord tumors has, as has been said, considerably improved since we have learned how to diagnose more accurately its segmentary location and to operate with favorable results. Both of these possibilities, however, chiefly exist in isolated, slow-growing intradural tumors. Of these a very large number have recently been successfully operated upon—Eskridge, Schulze, Allen Starr, Boettiger, Krause, and Oppenheim. Intramedullary cases are naturally not suitable for operation; also many of the extradural, because they are either malignant metastases, or involve a large portion of the spinal cord.

Therapy.—For surgical treatment intradural, extramedullary tumors are the most suitable. They are more easily diagnosed from intramedullary than I formerly thought. If in connection with long present unilateral root symptoms unilateral cord symptoms of the same side set in, it is tolerably certain that an extramedullary, usually intradural, tumor is present; and since at this time the general diagnosis of the tumor, according to recent experiences, is tolerably sure, even if no other tumors are present in the patient, operative measures may be instituted with the best hopes of a successful result. It is, of course, to be understood that in the presence of another tumor, the prognosis is always less favorable.

The most important therapeutical question is, At what time should one operate upon a tumor of the meninges? Here two things are especially to be considered: First, the segmentary location of the tu-

mor must be as accurately as possible diagnosed; second, it must be shown, with the greatest certainty possible, that the cord has suffered no irreparable injury through the tumor, for if such injury had been produced no improvement of the injured functions could be reasonably expected after the successful removal of the tumor. I have earlier advanced the view—perhaps somewhat too much on neurological grounds—that at first, so far as possible, a sure segmentary diagnosis should precede an operation, and that such a diagnosis could be made only when the compression of the spinal cord was tolerably pronounced. At present I still maintain the same ground; but in accordance with the new researches of Schultze, Allen Starr, Eskridge, Boettiger, Krause, and Oppenheim, I believe that too much stress should not be laid upon the absolute certainty of the segmentary diagnosis. If we wait for sure signs, all must be staked upon the result of an operation, which would have been very favorable if we had been bolder and had not delayed so long. The only reliable root symptoms which can here be employed are the atrophic muscular paralyses. Very much less useful are the pains which constitute the principal portion of the clinical picture, first, because they are purely subjective symptoms, and, second, because the most recent observations have shown that tumors of the meninges may give rise to pains far removed from the territory of the root lesion. However, since muscular atrophies dependent upon root lesions can be observed only in the territory of the brachial plexus and the lumbosacralis, in such cases the segmentary diagnosis can be sure only with a beginning compression of the cord.

In the dorsal portion of the cord the root symptoms are limited to the segmentary pains, which are uncertain. Here, if we would proceed on a sure basis, we must wait until the symptoms produced by the disturbances of the functions of the diseased segment appear. But this takes place only when complete compression occurs. In partial compression of the upper dorsal portion disturbances of sensation of the thigh may be entirely absent, and be present only in the feet and legs, so that following these symptoms the location of the lesion of the cord would be placed much too low. In spite of these errors of diagnosis, however, an operation should be done if the general diagnosis of a tumor is certain, and from the constant and permanent pains and the continuous hyperæsthesia, the segmentary location of the lesion can in some measure be judged. Atrophic paralysis of the abdominal muscles signifies a lesion of the lower dorsal segment (Oppenheim).

I refer those interested (in the large number of spinal-cord tumors which have been operated upon) to the "Jahresberichte für Psychiatrie und Neurologie," where I have described them in detail.

Hæmatomyelitis.

Traumatic hæmatomyelitis corresponds fundamentally to contusion of the brain, only that in consequence of the structure of the spinal cord hemorrhages into the gray matter extend upward for a greater or less distance and involve regions which are not directly affected by the traumatism. Naturally here they also produce destruction of the nerve substance. As the cause of central-cord hemorrhages in the cervical region and medulla oblongata, F. Schultze has recently drawn attention to the importance of severe labors—especially foot extractions and the production of Schultze's vibrations. Such manipulations may also produce injuries of the vertebral column and the vertebral ligaments.

The entire destruction of long portions of the spinal cord, resulting from traumatism, may be due to the hemorrhages caused thereby, as well as to primary necrosis. Such may also be produced by lymph stasis, and are also found in connection with tumors and other lesions which produce a gradual compression of the cord.

Traumatisms, which in any portion of the cord produce large and diffuse destruction, may give rise to unilateral or bilateral tubal hemorrhages above and below the lesion (Minor), which especially more or less involve the gray substance. These hemorrhages may produce symptoms which result from lesions above the portion of the cord originally involved in the traumatism. In unilateral cervical lesions a coincident unilateral tubal hemorrhage in the gray substance above the primary (chief) lesions may give rise to atrophy and partial anæsthesia of an arm, spastic paralysis of the leg of the same side without anæsthesia, and extensive partial anæsthesias of the opposite side of the body (Minor); also a clinical picture which closely resembles syringomyelia. If such tubal hemorrhages, unilateral or bilateral, are diffuse and cause the destruction of the entire cross section in the corresponding territory, there may be present complete motor and sensory paralysis and partial anæsthesia with or without muscular atrophies.

Poliomyelitis Acuta Anterior Infantum.

Etiology.—The spinal paralysis of children is quite frequently met with as a sequel of whooping-cough. In a case of poliomyelitis F. Schultze, by lumbar puncture, isolated the Fränkel-Weichselbaum diplococcus from the cerebrospinal fluid. The same organism has also been found in purulent cerebrospinal meningitis. Traumatisms are only very infrequently responsible for the spinal paralyses of children. Over-exertion is, perhaps, a more prominent causative factor.

Pathological Anatomy.—It is now generally conceded that the spinal paralysis of children is a genuine myelitis whose producer reaches the spinal cord through the blood. That a diffuse myelitis really exists can be demonstrated by the use of Marchi's methods of examination. An involvement of the cerebral nerve nuclei—especially the facialis or abducens, and convulsions, are most frequent in the epidemic form of the disease. Under these conditions there is present a limitation of the paralysis to certain brain nerves in regard to the significance of which there can be no doubt.

Symptomatology.—Researches of the last few years, especially in inflammatory (exudative) lesions of the central nervous system, have shown that a recovery in an anatomical sense is here possible; or at least reparative processes, which approach such a recovery, occur. Not infrequently a triplegia is also present—for example, a paralysis of the shoulder muscles of one side and an asymmetrical paralysis of both legs.

Oppenheim says that in rare cases only partial degenerative reactions are present in permanently paralyzed muscles. In later life in the spinal paralysis of children there are observed not only progressive muscular spinal atrophies but also primary muscular dystrophies and diffuse myelitis.

Diagnosis.—In neuritis the paralysis eventually is nearly or entirely symmetrical, while in poliomyelitis a striking asymmetry is present. Small children may have slight traumatism of the shoulder-joint and absolute immobility of the arm ("Hemmungs-Lähmungen," Vierordt). Complete recovery usually elucidates the diagnosis; furthermore, poliomyelitis is not very frequent during the first months of life.

Very closely related are those cases which Oppenheim describes as the extensive myotonia or myohypotonia of childhood. He also found in some of these cases an absence of the tendon reflexes and a reduction in the electrical reaction—no degenerative reactions. Complete paralyses, moreover, were infrequent. The absolute symmetry differentiates these cases from poliomyelitis; at least, complete paraplegias of a long duration are seldom seen in poliomyelitis.

Syringomyelitis, which is infrequent in childhood, is differentiated from poliomyelitis by its disturbances of sensation; hereditary muscular defects may be easily differentiated by careful examination.

Therapy.—Great results in the rectification of the deformities and disturbances of function resulting from the spinal paralysis of children have recently been obtained by the methods of tendon transplantation inaugurated by Nicoladoni and Drobneck, and principally carried out by German orthopedists (Vulpius, Lange, Hoffa, Franke). The principle of the method is that the action of paralyzed muscles is replaced by the action of sound muscles whose tendons are artificially

united with those of the paralyzed muscles. It is necessary for the success of this method that only such sound muscles be employed as normally move the affected joint, and that all the muscles of the joint are not paralyzed.

It has recently been shown that it is possible to substitute the tendon of a sound muscle for that of a paralyzed muscle, although these muscles act in direct opposition to one another. If, as shown by Lange, these tendons are not long enough for such a union, they may be extended by prolonging them with silk threads. There are various methods of tendon transplantation. The descending method (Vulpius) consists in dividing the tendon of the sound muscle transversely and uniting it to the tendon of the paralyzed muscle. In the method which Vulpius calls "ascending" and Hoffa "positive," the sound muscle is not divided. The tendon of the paralyzed muscle is divided and united by its upper extremity to the sound muscle. Finally—and this method is used principally when operating upon the tendo Achillis and the flexors of the knee—the tendon of the sound muscle is only partly divided, the divided portion being united to the paralyzed muscle.

These operations are most frequently performed in the region of the ankle-joint, because the deformities are most common here.

The results of tendon transplantation have been improved by producing a shortening of the tendon of the paralyzed muscle and a lengthening of the tendon of the sound muscle; by this method a more complete correction of the deformity of a paralyzed joint has been obtained and the sound muscle given a better opportunity to carry out its function.

Finally, Lange, observing that the tendon of the paralyzed muscle frequently suffered from malnutrition, and, after its union to the sound muscle stretched and thus made the result of the operation but temporary, has advised that the tendon of the sound muscle be not united to that of the paralyzed muscle, but implanted in the bone at or near the site of the insertion of the paralyzed muscle (periosteal method).

Although the results of tendon transplantation have been very brilliant in the treatment of hitherto hopeless deformities, cases are not very rare in which all the muscles of a joint are paralyzed or in which only a single small muscle remains intact. Here the method is entirely useless or followed only by unsatisfactory results. In all cases the neurologist and surgeon should work together in this difficult field. Only by electrical tests can it be determined, in most cases in children, what is the condition of the muscles. This examination is very difficult and, even for the experienced electrodiagnostician, not always possible. Some orthopedists claim that even paralyzed mus-

cles may regain their functions if only by a suitable operation a possibility for the exercise of such a function is given.

Also in complete flail-joint the attempt has been made to substitute a shortening of all the tendons for arthrodesis. But arthrodesis cannot be entirely dispensed with. Hoppe has frequently done a tendon transplantation upon one foot and an arthrodesis upon the other. There is a misprint in my original article (Vol. XI., p. 710). It should there read that by arthrodesis in the knee- and ankle-joints a tolerably useful limb may be obtained only when in the hip-joint the ileopsoas is still sound. But the hip-joint should not be ankylosed.

Acute Myelitis.

Definition and Pathological Anatomy.—It is difficult and hitherto impossible exactly to define and limit the condition that should be called myelitis, because the anatomical basis of the inflammation is very variable; and especially with respect to spinal-cord inflammation, nearly all the macroscopical and microscopical appearances which have been found in myelitis are not specific for this disease, but are also present in other non-inflammatory spinal-cord diseases (traumatism, simple œdema, compression, ischæmia). Thus the anatomical picture alone—the microorganisms found infrequently in the spinal cord, and also the lesions of disseminated myelitis—almost never establishes a diagnosis with certainty that the disease of the medulla is of an inflammatory nature. For this reason I regard it as proper to consider the etiology together with the anatomical diagnosis of spinal-cord inflammation, and especially to regard such diffuse lesions of the spinal cord as "myelitis" as are produced by infections or intoxications.

Since 1897 a large number of observers have undertaken an extensive and very careful study of the pathological anatomy of myelitis, but without much result with respect to the foundation principles.

Schmaus states that myelitis can be divided into three histological forms. The first form shows a swelling of the nerve tissue and glia resulting from an œdema. He describes this as the parenchymatous-degenerative form of myelitis. In the second form the vessel changes are the most prominent feature of the histological picture. Hemorrhages from the diseased vessels are especially prominent in this form. In the third form there is a complete softening of the cord; in the detritus nucleated cells are especially prominent. A cavity may finally be formed in the cord. Marinesco believes that the myelitic poison operates indirectly through the blood-vessels or directly upon the nerve tissue; he has in a large number of cases demonstrated the presence of microorganisms in the spinal cord. Redlich comes to my

conclusion: "there is no single absolutely sure characteristic of myelitis."

From the above summary of the views of certain observers with respect to myelitis, it is evident that the view expressed by me five years ago, that from the anatomical picture in a given disease of the spinal cord it is not possible to say that it is inflammatory, must still stand.

Although the recent anatomical researches have not definitely determined the nature of myelitis or given grounds for a exact anatomical diagnosis, a large number of new facts have been brought to light by the newer methods of research, and many of the appearances which have been known for a long time have been more accurately studied.

Schmauss gives the following anatomical classification of acute myelitis: 1. Myelitis transversa, in which the entire cross-section of the cord is involved, the longitudinal involvement being not too great, and in which the white substance is more affected than the gray. The large deposits may be composed of several smaller ones. This is more frequent than the presence of a single deposit (Mager). 2. Meningomyelitis. 3. Poliomyelitis. Thereto also belong cases which are designated as central myelitis, which are characterized by a rapid extension of the process superiorly or inferiorly—myelitis generalis or diffusa; the most frequent example of this type is Landry's paralysis. 4. Disseminated myelitis or encephalomyelitis. 5. Purulent myelitis or abscess of the spinal cord.

Etiology.—Strümpell in general agrees with Marie and the other authors who hold that myelitis always has an infectious or toxic etiology, and that thus it is never a primary, but always a secondary process. In cases of severe blood diseases in which the pathological condition is coexistent with a disease of the spinal cord and dependent upon the same factors which produce this or upon some other unknown cause, the myelitis, as a rule, involves only the territory of the peripheral blood-vessels and produces a non-symmetrical lesion of the posterior and lateral columns. Finally, in any portion of the cord the deposit may become confluent and produce a transverse myelitis. The symptoms are: first stage, pains and paræsthesias, especially in the hands and feet; second stage, ataxia, especially of the legs; third stage, paraplegia with spastic paralysis, finally flaccidity of the muscles; bladder and rectal disturbances; muscular atrophies.

Symptoms.—In transverse lesions of the spinal cord, which are located high, the muscles whose nuclei lie below the lesion finally atrophy considerably; thus, for example, those of the leg in dorsal myelitis. However, qualitative electrical disturbances are not found in these muscles. A marked reduction or absence of the electrical reaction is often preceded by a pronounced increase in the resistance of the skin to electricity, which is produced by subcutaneous œdema

or marked hardening of the skin. This resistance can be overcome by the galvanic current; the faradic is less effectual.

Diagnosis.—For the diagnosis of a genuine infectious myelitis the examination of the cerebrospinal fluid, obtained by lumbar puncture, is of importance. Strümpell in a case of transverse myelitis found a cloudy cerebrospinal fluid which contained leucocytes and the staphylococcus albus.

The differential diagnosis between a transverse myelitis and an hysterical spastic paraplegia is often difficult. Of especial importance is the presence in hysteria and neurasthenia of increased tendon reflexes and often a genuine Achilles clonus. However, usually the Achilles clonus present in hysteria is neither so marked nor so prominent as that met with in organic conditions. Very important for the differentiation of an organic lesion is the fact that in such cases irritation of the sole of the foot causes a dorsal flexion of the great toe with coincident flexion or extension of the other toes (Babinski's phenomenon).

Disseminated encephalomyelitis is especially met with in childhood. Accordingly its differential diagnosis from progressive paralysis is made less difficult.

Therapy.—Kocher warns against emptying the bladder by expression, because thereby may be caused injury and ulceration of the vesical mucous membrane. The catheter is always to be preferred.

Chronic Myelitis.

Although a very rare disease, nobody is inclined entirely to exclude chronic myelitis from neurology. Even Strümpell, who is most strenuous in his views, and who is the most qualified to speak upon the subject, is obliged to admit that toxic influences under certain conditions work very slowly upon the spinal cord, usually in a diffused and disseminated manner; that here all transitions from acute to subacute and chronic myelitis are seen; also here are found all combinations between isolated and diffuse lesions of the spinal cord (pseudo-system lesions). Here especially belong pellagra, ergotismus, lathyrismus, and possibly rabies; also the intoxications which are caused by poisonous metabolic products, as in diabetes, and finally those diseases of the spinal cord in which severe blood changes are present. Usually there is present here a pseudo-system lesion of the posterior and lateral columns in the region of the peripheral vessels; a similar clinical picture is also present in chronic meningitis. Oppenheim regards a chronic process which supervenes upon an acute process as a chronic myelitis.

Softening.—This may occur through ischæmia following closure of

the vessels, and indeed in very chronic processes such ischæmic softening is more frequent than in acute, and moreover is difficult to differentiate from the true inflammatory processes. According to Schmauss, there are chronic processes in the spinal cord which so follow the course of the vessels that their myelitic nature must be regarded as certain. Here especially belong those met with in system diseases.

Diagnosis.—The diagnosis of a chronic transverse myelitis can be made only by exclusion and is then seldom sure. All compressions of the cord are to be excluded, also syringomyelia and multiple sclerosis. If, however, multiple sclerosis is regarded as inflammatory in character, those cases in which the lesions are limited to the cord can be as well considered myelitis as multiple sclerosis. The character of intramedullary tumors is often very difficult to determine, and it is also difficult to differentiate them from chronic myelitis; many of these tumors grow very slowly, and possibly for a long time may remain *in statu quo;* here the specific tumor symptoms, especially the long-continued pains, may make an insignificant part of the clinical picture.

Abscess of the Spinal Cord.

Schmauss calls abscess of the spinal cord a purulent myelitis. Almost always the purulent process extends from the meninges into the spinal cord; according to Schmauss, they preferably enter the cord through the tissue of the posterior horns and extend to the gray substance of the anterior and posterior horns. Their diffusion is analogous to that of the hemorrhagic deposits (tubal hemorrhage). Gonorrhœa, especially gonorrhœal cystitis, is of great importance in the etiology of abscesses of the spinal cord.

TABES DORSALIS.

BY

PAUL J. MÖBIUS,

LEIPSIC.

IN the following pages I shall review briefly the advances in our knowledge of tabes since 1897, at the time when my article on this subject in Vol. XI. was prepared.

Etiology.—The belief that tabes is of syphilitic origin is constantly gaining ground. This view has not indeed as yet found universal acceptance, but its opponents can do nothing but repeat their former arguments, and by such repetition seek to cover up the defects in their reasoning. E. v. Leyden still holds to the old ideas, and his followers advance weak arguments against the syphilitic origin of this disease. Others discuss the points involved without providing themselves with sufficient information. Thus Virchow demonstrated that he had not given the clinical aspect of the question due consideration. Recently Gläser has written an entire book on the subject, basing his conclusions upon old hospital experiences, although all intelligent persons know that such material is absolutely worthless for the decision of the questions involved. When we consider the rapid advances in scientific observation made during the last few years it is surprising that most observers, although they acknowledge the syphilitic origin of tabes in the majority of instances, still do not regard it as the *conditio sine qua non* for the development of the disease. This does little credit to the reasoning of those who hold this view, for it is manifestly absurd to suppose that in nine cases of tabes the causative factor is the poison of syphilis introduced into the body, while in the tenth case totally other agents play the etiological rôle.

Many observations have demonstrated that hereditary influences play an important part in the etiology of tabes. It is astonishing how often both parents have suffered from this disease, or one has had tabes while the other has been afflicted with progressive paralysis, and it is apparent in such cases that syphilis has been the only causative factor.

Tabes has been frequently observed in childhood. In such cases inherited syphilis is always responsible for the development of this disease, and it is readily ascertained that one of the parents, usually the father, is syphilitic. It is striking that very often in the tabes of young adults a personal history of syphilis is present. This fact, together with the frequency of an hereditary history in these cases, leads to the conclusion that under certain conditions special poisons are developed in the bodies of syphilitics, poisons which have a special deleterious influence upon the nerve tissues.

Edinger has drawn attention anew to the influence of overexertion as an etiological factor in this disease. A great multitude of men overexert themselves and many poison themselves with alcohol, lead, mercury, and other poisons, or develop inflammatory rheumatism, typhoid fever, pneumonia, and other infectious diseases; but tabes never occurs as a sequel in such cases. Only in those in whom a syphilitic history, either personal or hereditary, is present does tabes develop, and often in these cases it does so independently of whether or no overexertion has taken place. The soldier, the laborer, and the housewife all may have inflammatory pains in the bones, and bladder disturbances, yet in all (unless tabes is present) the knee and pupil reflexes are preserved. Many women develop tabes, although they have lived in the greatest ease and have been subjected to no overexertion, and they show the same symptoms which appear in the laborer and those who have experienced great privation. It is indeed true that at times certain cases may show special symptoms according to the special occupations in which the patients have been engaged. Thus in singers laryngeal symptoms are often apt to be especially prominent. It is thus true that the symptomatology of tabes may vary according as different parts of the body have been excessively used. It is further true that overexertion can hasten the development of the disease, and the first appearances may be in those portions of the body which have been especially active or injured. Thus the initial pains appear earlier in a limb, the bones of which have been broken, than in one which is perfectly sound. There is no doubt that local inflammatory lesions are especially injurious to those suffering from tabes.

Pathological Anatomy.—There appears to be no doubt that the chief lesion in this disease is localized in the fibres issuing from the posterior roots of the spinal cornua, and that this lesion is a primary atrophy. It is very probable that other fibres are also involved, but in general it can be said that there is no uniformity in these secondary lesions. Many researches have shown that the spinal ganglia are but little if at all involved, and also that the changes in the posterior fibres are not of a secondary nature as is the case in lesions of the anterior fibres in acute poliomyelitis. The endeavors to localize the

lesion responsible for the reflex pupil changes have as yet been without result.

When tabetic paralyses are present degenerative changes are found in the motor neurones. In some cases the cells themselves are involved, while in others the protoplasmic prolongations are chiefly affected. In paralyses of the eye muscle the cells in the corresponding centre show degeneration. In the case of other paralyses L. Schaffer has shown that degenerative changes are present in the cells of the anterior horns. During the last few years the tertiary lesions of syphilis have been frequently found post mortem in those dead from tabes. Dinkler has especially drawn attention to the fact that the meningeal changes in tabes are entirely similar to those observed in syphilis and that the same are not observed in syringomyelia, multiple sclerosis, etc.

Symptomatology.—P. K. Tell has given the name "ocular crises" to the periodical attacks of pain which frequently occur in the eyes. There is photophobia, and the eyes are much suffused with an excessive secretion of tears. Jullian has also described "nasal crises" which are accompanied by violent attacks of sneezing and hypersecretion of the nasal mucous membranes. The observations of Hitzig and Löhr, that very early in the disease there is present a complete or partial cutaneous anæsthesia of the trunk between the waist and the thorax, have been generally confirmed. Abadie and Roiher have shown that at times the cornea largely loses its sensibility to finger pressure.

The various reflexes have been studied by a large number of observers. Babinski has shown that the tendo Achillis reflex is at times entirely absent, when the patellar reflex is completely preserved. Frenkel states that the reflexes of the upper extremity are absent very early in the disease. Others have shown that the reflexes which have disappeared may subsequently for a time return.

Paralyses of the involuntary muscles have been repeatedly observed.

Westphal and Piltz have recently described a pupil phenomenon which bears their name. It consists in the narrowing of the pupil of one eye when the lid of the other eye is closed by the hand of the observer. This occurs in diseases other than tabes, but is especially pronounced in cases in which the pupil reflexes are lost.

J. Abadie has given a description of the clinical alterations of the vertebral column. As a rule, there is a progressive kyphosis with fixation. Fractures of the vertebræ have been observed. They may be produced by the ordinary movements of the body.

In tabetic patients with trigeminal anæsthesia Giraudeau and Thibièrge have observed characteristic ulcers of the involved region. These are superficial, non-inflammatory, and painless. Their base is smooth, of a reddish-gray color, and easily bleeds.

According to P. Marie, the body temperature in tabes, as a rule,

is subnormal. In six out of ten cases it varied between 36.2° and 36.8° C. (97.1° and 98.2° F.).

In many cases there is a marked and progressive reduction in the body weight. This occurs without apparent cause and in the absence of pathological lesions in the various organs. In those cases in which the loss of appetite is very marked the body weight falls rapidly. Often a characteristic cachectic condition develops and permanently remains. In other cases the normal weight is subsequently nearly regained without apparent cause. One of my patients in five months lost 18 kgm. (nearly 40 lbs), but this was eventually entirely regained.

The *treatment* of tabes may be considered under two heads: (1) antisyphilitic, (2) Frenkel's method (non-antisyphilitic). Opinions are divided in regard to the value of mercurial treatment in tabes. It may be said that the ocular symptoms are improved by this drug, but that the general condition is not benefited, and may be harmed thereby. I believe that the careful administration of mercury in tabes is without danger, but that the course of the disease is not in any way influenced. I therefore advise its use only in those cases in which tertiary syphilitic symptoms are plainly evident.

The idea that the administration of mercury in syphilis prevents the subsequent development of tabes is erroneous. In reality tabes follows syphilis independently of whether it has been properly or improperly treated with mercury.

Frenkel's method is, properly speaking, not a treatment of tabes, as it entirely concerns itself with the ataxia. In general it may be said that this treatment is unsuitable for use by the majority of physicians, as its successful application requires much experience and great care.

DISEASES OF
THE PERIPHERAL NERVOUS SYSTEM.*

BY

JAMES HENDRIE LLOYD,

PHILADELPHIA.

ALTHOUGH only six years have elapsed since the publication of the article in this work devoted to the diseases of the cerebrospinal and sympathetic nerves, a large number of contributions have appeared in medical literature on this subject. In attempting to present the subject again the object is not to go over it anew, but simply to bring it up to date in a practical and thorough manner. Consequently no attempt is made at an exhaustive or complete résumé of the recent literature. On the contrary, a selective plan has been pursued by which those contributions alone have been reported which seem to present some novel features.

The science of neurology, as is well known, is one of the most progressive while one of the most unsettled in the whole domain of scientific medicine. While most of its principles, both of pathology and diagnosis, are thoroughly well established, there yet remains a large amount of work to be done to clear up obscure points in both these fields. The peripheral nervous system, it is true, is in many respects the simplest and easiest department of nervous diseases to describe and to treat. But still even here the main subjects of pathology are just as unsettled as in the central nervous system. This is strikingly shown in that most important of all subjects, the repair and degeneration of diseased and divided nerves. I have thought it best to devote considerable of the allotted space in this book to a fairly full discussion of the subject of nerve regeneration, and this subject will now be the first which will occupy our attention.†

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* A somewhat extensive bibliography appended to the manuscript of this article has been omitted by the editor for lack of space.

† The author has to acknowledge the assistance of Dr. A. J. Ostheimer in preparing this section.

Regeneration of Nerve Fibres.

There has been an endless division of opinion on the important subject of regeneration of divided nerve fibres. Surgeons, relying upon their practical observations, have always maintained that the cut ends of a divided nerve can regenerate much earlier than has been allowed by the pathologist. They have judged entirely from their practical results, and it must be conceded that the value of these practical observations far outweighs any mere theoretical consideration. In other words, one positive observation is worth more than a great body of negative proof. Pathologists, reasoning partly but not entirely from theory, have maintained that the peripheral part of a divided nerve undergoes rapid degeneration after section, and that it cannot possibly regain its function until this degenerated nerve fibre has been replaced. The contention has lately narrowed itself down to the question as to how and where this exact regeneration occurs. To judge from the experimental work of some pathologists, we should be obliged to believe that the regeneration of the nerve occurs by a proliferation of the proximal end alone; that from this end new fibres arise by a process of budding, and that these new fibres gradually find their way even through scar tissues if this is not too dense, and so replace in time the degenerated fibres of the distal segment. Such a process of repair must of course be most tedious, and in many cases it seems to be impossible; but the experimental work of such men as Stroebe seems to demonstrate that such a process does occur. That this theory, however, does not explain all cases is evident, and the tendency has been lately to recur to the old and for a time abandoned theory that the nerve fibres in the distal segment of the nerve, although entirely separated from the neurone body, can undergo a process of regeneration from the cells of the sheath of Schwann. This idea has been revived lately, especially by the observations of Bethe. The views of some of the most careful observers are given below.

Kennedy's conclusions in regard to the regeneration of nerves are as follows:

I. Deductions from the results of operations: The author from his results concludes that the early return of sensation must be regarded as indicating a restored conductivity of the divided nerve. He holds that the theories which have hitherto been advanced to account for early return of sensation, apart from reunion of the nerve, are inapplicable to cases in which *early* return of sensation occurs from suture, performed after the lapse of *several months* from the time of section. The imperfect return of motion he takes to be fully explained by the fact that the muscles have undergone great trophic change, or indeed,

total destruction, and that therefore their restitution must be slow, or may even be impossible.

II. Deductions from the microscopical examinations: 1. *Degeneration:* (*a*) That there is no evidence of ascending degeneration of the kind described by Krause after interruption of a nerve. (*b*) That the old axis cylinder and myelin sheath are destroyed in the peripheral segment, and in the ultimate portion of the central segment.

2. *Regeneration:* (*a*) That young nerve fibres are developed in the peripheral segment as well as in the end of the central segment, and even while there is no connection between the two ends. (*b*) That these young nerve fibres originate within the old sheath of Schwann from the protoplasm and nucleus of the interannular segment. The spindle cells formed from the protoplasm and nuclei of the interannular segments elongate and unite to form protoplasmic threads, with the elongated nuclei attached to their sides. The central portion of the protoplasmic thread develops into the axis cylinder, while myelin is deposited in drops in the protoplasm surrounding the newly formed axis cylinder. The protoplasm in which the myelin is deposited remains with the nucleus as the neuroblast of the new interannular segment. (*c*) That so long as conductivity of the nerve is not reëstablished, the development of the fibres proceeds only to a certain stage; and as the new fibres three and eighteen months subsequent to division present identical characters, this stage may be regarded as a resting stage, depending for its further development on reëstablishment of function. (*d*) That cicatricial intercalary segments reuniting the ends of a divided nerve may be permeated by young fibres from end to end without reëstablishment of function, if the amount of cicatricial connective tissue present in the mass is sufficient by its pressure to prevent the passage of impulses.

Fleming concludes his article on "peripheral neuritis with comparative results of experimental nerve degeneration and changes in nerve cells," as follows: The fine medullated fibres, which appear to play an important rôle in "ascending degeneration," degenerate very early in peripheral neuritis, and are associated with marked vascular changes. The comparative absence of the vascular changes in Wallerian degeneration is evident from an examination of my series of specimens. The limited nature of the vascular changes in the central end of the divided sciatic in dogs and rabbits, and in the nerves of stumps in man suggests not merely the relationship of fine medullated fibres to the vessels, but is also a strong contrast to the great vascular changes found so frequently, at least, in peripheral neuritis. Peripheral neuritis is different from either ascending or descending degeneration, and is manifestly caused by a toxin acting on cells as well as nerve fibres, and possibly vessels.

Huber reports the results of his experiments in regard to the degeneration and regeneration of motor and sensory nerve endings in voluntary muscle. He comes to the following conclusions: 1. The motor and sensory nerve endings of voluntary muscle degenerate after severance of the muscular nerves. The motor nerve endings and the extreme distal portion of the motor nerves degenerate earlier than do the sensory nerve endings. 2. The motor and sensory nerve endings in voluntary muscle may under suitable conditions regenerate completely. The motor nerve endings regenerate more quickly than the sensory nerve endings. 3. These experiments show clearly that the regeneration of a degenerated portion of a peripheral nerve and its termination is brought about by the down growth of the axis cylinder of the central undegenerated portion of the nerve fibre.

Kennedy contributes an article on the restoration of coördinated movements after nerve section; and the conclusions from the physiological and histological results of his experiments are as follows:

1. After section and immediate coaptation of a nerve, restoration of conductivity and of voluntary function may be effected in a few days.

2. This early restoration of conductivity need not be the result of the union of the old nerve fibres, *i.e.*, reunion by so-called first intention or without Wallerian degeneration; but may be the result of regeneration of young nerve fibres in the peripheral segment.

3. Voluntary coördinated movements are regained equally soon, whether the two ends of the divided nerve are united as accurately as possible so as to bring the corresponding ends of the nerve fibres into contact as nearly as possible, or whether, previous to reunion, the peripheral segment is twisted so that when united to the central segment non-corresponding ends of the nerve fibres are brought into contact.

4. In the latter case the microscopical examination of the seat of reunion leaves it doubtful whether the restoration of function is due to the reëstablishment of the old paths by decussation in the nerve cicatrix or to the reunion of ends of nerve fibres which do not correspond, but which happen to be brought into apposition.

5. In suturing a divided nerve no trouble need be taken to secure coaptation of the two segments in old relationship, simple approximation of the two ends being all that is required.

Baer, Dawson, and Marshall concluded from their experiments on dogs that after severance of the fibres of the dorsal roots of the spinal nerves between the ganglion and the cord, regeneration of the fibres into the cord will take place under proper conditions (quoted by Spiller). They did not express a positive opinion as to the completion of the regeneration, and there are seven experiments showing

great differences in the rapidity of the process. They naturally conclude that if the root fibres can be regenerated in the posterior column of the cord, the fibres in the other tracts of the central nervous system will also regenerate. This observation refers to the spinal cord.

Fickler, who has gone over this subject, claims that others have not found any regeneration of the nerve fibres worthy of the name after the division of the spinal cord. Among the most important observations, as will be seen, are those of Bethe. After resecting the sciatic nerve of the dog and sewing the peripheral stump within the muscle to prevent union of the two ends, he observed the proximal end of the nerve to degenerate, but that later full regeneration of the peripheral portion occurs from the nuclei of the sheath of Schwann. That this was true nerve fibre seems to be proved by the fact that the irritation of it caused contraction of the muscles. This regenerated fibre differs in no way from normal, and yet it was not in continuity with the neurone body. A very curious observation of Bethe's related to the fact that if this regenerated peripheral nerve were again cut its peripheral portion below the line of division degenerated, but the more central portion persisted, even though it were not in connection with the nerve cell bodies (quoted by Spiller). It is evident that those observations by such a careful experimenter and histologist as Bethe must have a powerful influence in modifying the views of pathologists as to the regeneration of nerves. They are probably the most important observations that have been contributed to the subject in recent times. Whether or not they are to be verified remains to be seen, but the unqualified statement of Bethe that the divided nerve fibre can regenerate from the nuclei of the sheath of Schwann, irrespective of whether or no reunion had occurred between the divided ends of the fibre, is not to be lightly ignored. If this revived view—for it is an old view revived—should prove true, it will in a sense be a triumph for the surgeons. As is said above, they have contended from their practical experience all along that divided nerves regenerate and that function is restored much more rapidly than pathologists and histologists were willing to admit.

One of the most important of recent contributions to this subject is the monograph by Ballance and Stewart on the healing of nerves. After reporting a series of carefully performed experiments they review this subject briefly, and unhesitatingly declare their adherence to the opinion that the process of regeneration takes place by outgrowth of the new axis cylinder from the cells in the neurilemma or sheath of Schwann. They classify the controversialists in two schools, which they term the "Central" and "Peripheral." To the first of these belong Waller, Ranvier, His, Kölliker, Howell, Huber, Notthafft, Stroebe, Vanlair, Gürwitsch, Kolster, and Harrison. On the other

hand, the peripheral school claim such adherents as Tizzoni, Cattani, von Büngner, Kennedy, Bethe, Galeotti, Levy, and Engelmann. The process of regeneration in the distal segment, according to Ballance and Stewart, takes place somewhat in the following way: The new axis cylinder is propagated by the deposition along one side of the spindle-shaped neurilemma cell of a thin thread, which grows in length until it projects beyond the lines of the parent cell. Thus within each old neurilemma new fibres are laid down in short lengths. These afterward become continuous so as to form the regenerated axon. This process is described by them in minute detail, and their description is based upon observations which seem to be most careful and exact. The process occurs even before the distal and proximal segments have been united. The new fibres, however, are somewhat slower in growth if the distal segment has not been united to the proximal. It is thus seen that this doctrine is entirely subversive of the theory that the new axis cylinder must be an outgrowth from the old axis cylinder in the proximal segment. These observers call attention to some of the effects of their observations upon the neurone theory. In their opinion the neurone theory, in so far as it bears on the peripheral nervous system, must be discarded. The peripheral nervous system, to use their language, must be considered to be made up of chains of cells, set end to end, whose axis-cylinder processes fuse together to form continuous paths in the peripheral nerves.*

The presentation which we have given above probably covers the most important ground which has been gone over in neuropathology in the last six years. Its importance cannot be overestimated. If we are in the presence here of a newly recognized fact with regard to the ability of the nerve fibres to regenerate, we should not allow mere theory to prejudice us against it. It is certain that we can no longer dogmatically affirm that it is impossible for the divided portion of a nerve fibre to regenerate, unless we reject the views of Bethe especially, and some few others, until they be proved by further research. In estimating the value of Bethe's observations, if they are found to be accurate, we should not fail to give credit to some of the older observers. As said in our article in a preceding volume of this work, many of the surgeons especially have maintained that this regeneration of nerve fibres in the distal segment can and does take place before union with the proximal end. Bowlby especially maintains this view in his work on "Diseases of the Nerves," expressly stating his belief in

* This work by Ballance and Stewart contains a valuable bibliography, and as we have already stated in the text, is the most important recent contribution to this subject. That its tendency is revolutionizing is very evident. It supports the contentions of the surgeons who in the past have claimed that they obtained results which were apparently contrary to the teachings of the histologists.

the early formation of the new nerve fibres from nuclei in the sheath of Schwann. This view, in fact, is rather an old view, so that it will not do, if it prove true, to give the whole credit to Bethe. It seems, however, that this latter observer has made rather more accurate and convincing observations than his predecessors. Bowlby even claims that he found nerve fibres in the distal portion of the nerve as late as seven and nine months after division. The idea then expressed that these fibres were preserved intact from the time of the section can now be seen to be probably erroneous, for they might have been regenerated in the manner here described. In discussing this subject we then said that the facts of surgery and of experimentation must conform to the facts of histology before they can be accepted. But it may be necessary to remodel this sentence somewhat so as to say that the theories of histology must be made to conform to the facts of surgery and experimentation.

Recent Work on the Gasserian Ganglion.

Spiller has done considerable work in the histological examination of some of the Gasserian ganglia which have been excised by surgeons for the cure of tic douloureux. In one ganglion excised by Dr. Cushing, he found the nerve cells diseased. Many of them were intensely shrivelled, and stained deeply. He does not claim, however, that the degenerated condition of these nerve cells proves that the primary lesions of trifacial neuralgia are in the Gasserian ganglion. The diseased cells were not confined to any one part of the ganglion. In one case the sensory root was normal. In another case most of the nerve cells appeared to be fully or nearly normal, but some were deeply stained and much shrivelled. Most of the cells completely filled their capsules, and the peripheral portions of the cells contained fewer chromophilic elements than the central portion.

In an interesting case of endothelioma of the Gasserian ganglion, reported by Dercum, Keen, and Spiller, the latter observer made the histological report of the tumor. The growth consisted of endotheliomatous tissue. Altogether it may be said that these findings of Spiller, except, of course, in the case of the neoplasm just reported, consist chiefly of alterations in the bodies of the neurones, but that these changes cannot be regarded as characteristic or as proof that the initial lesion of tic douloureux is in the ganglionic bodies.

An interesting case is reported by Spiller and Frazier, in which the sensory root of the trigeminus was divided for the relief of tic douloureux. This operation was done at the suggestion of Spiller, who thought that if it could be shown that the sensory root of the

Gasserian ganglion does not unite after its fibres are divided, we should have a fact of great importance as indicating such an operation. Division of this root would be a less severe operation than the removal of the entire ganglion, and might have the same effect for the relief of pain. Dr. Charles H. Frazier performed this operation successfully. He had previously experimented by cutting the sensory root of the trigeminal in a large number of dogs. The results in the case of the dogs were examined microscopically. The observers were not able to determine any attempt at regeneration in the sensory root of the trigeminal nerve. But these cases do not disprove the possibility of such a regeneration. Spiller reviews the literature with reference to the regeneration of nerves, some of which has already been reported above. He believes that in view of the uncertainty of the regeneration of the sensory root of the trigeminal nerve, and of the great mortality attending the removal of the Gasserian ganglion, the division of the sensory root for the relief of tic douloureux is a justifiable procedure. The patient upon whom the operation was performed was a man aged sixty-eight years, who survived the operation without any alarming complication, and who at the end of a few weeks still presented an area of anæsthesia in the territory supplied by the fifth nerve. The pain had been relieved. No corneal ulcers had formed. It will be necessary, of course, to wait for some time before final judgment can be given in this case.

Coenen reports the microscopical findings in fifteen Gasserian ganglia removed by Lexer. In two cases no previous operation upon the peripheral nerves had been performed. These two ganglia were quite normal. This finding agrees with Monan's observation. The ganglia in the other twelve cases (one ganglion was misplaced and not examined) showed characteristic changes of their cells, and the changes in all cases were about the same. They consisted in swelling and vacuolization of the cells, fine granulation and rarefaction of the tigroid, even to complete tigrolysis; finally, in atrophy, chromophilia, pyknosis, and final disappearance of the ganglion cells, which was followed by compensatory growth of the connective tissue. The author is inclined to believe that the changes in the ganglia described were secondary, caused by the previous operations on the peripheral nerves.

Cavazzani reports his third case of rebellious trigeminal neuralgia cured by resection of the cervical sympathetic. The benefit was not immediately apparent in any case, but became more and more pronounced with the lapse of time.

Barber reports a case of pure tic douloureux relieved by 0.1 mgm. dose of aconitine given every four hours until the patient had taken ten granules, followed by iron and simple tonics. The conclusions he

deduces are: (1) " That aconitine does really seem to be a specific, and (2) that its action must be maintained by a restorative."

McConnell reports a case of neuritis of the fifth nerve with herpes and eczema. Herpes zoster occurring during an attack of neuritis of a portion of the ophthalmic division of the fifth nerve was first diagnosticated; later an eruption of acute vesicular eczema appeared, probably dependent upon the same cause as the herpes. The acute symptoms lasted three weeks. The patient had had an attack of "shingles" years before and had completely recovered. The eczematous eruption was confined to the distribution of one nerve. Influenza was thought to be the cause of the neuritis.

Gallemaerts reports a case of neuroparalytic keratitis, consequent upon a resection of the Gasserian ganglion. The case was a chronic one.

Keen and Spiller report three cases of peripheral resection of the fifth nerve for tic douloureux. In one case the supraorbital and infraorbial nerves were resected, and in the other two cases the infraorbital and inferior dental nerves were removed. "In spite of only the transitory relief, I believe it is wise to do these peripheral operations until the mortality of Gasserian operations has been materially lessened. These peripheral operations ought to be done early before the disease has had time to invade the ganglion. Very early operations—say after a month or two of ineffectual medication—might even cure permanently."

Schwabe contributes an article on the pathology of trigeminal neuralgia, with a report of the microscopic examination of two Gasserian ganglia. Krause first investigated the pathology of trigeminal neuralgia by the microscopic study of four Gasserian ganglia removed by him, and examined by Sanger. Since then about twenty ganglia have been examined after their removal for trigeminal neuralgia. The pathological findings in these cases, as a whole, may be divided into groups as follows: " In a few cases the ganglion was found to be absolutely normal. Of this group not much can be said except that a certain doubt must always be felt in any report of an absolutely normal condition of a ganglion so pathological in its manifestations as the ganglion in a case of persistent trifacial neuralgia of long duration, for it is assumed that only in such cases was an operation performed. A second group shows evidence of neuritis and degeneration so pronounced that there can be no question that this must be considered in any explanation of the pathology of this disease which may be attempted. The third group, composed of Spiller's one case, and the second one of mine, shows an interstitial inflammation. A fourth group, composing the largest number of reports, shows nerve-cell changes of various degrees of severity. In all of them, however, the

changes are less those of a primary cell affection than a secondary one. It must be admitted that these cell changes of themselves would form an insufficient basis for the pathology of the disease. The presence of brain sand was noted in three cases in the second of my series. In all probability this sand has no vital importance. In a very few cases changes in the blood-vessels were noted."

In the first of the two cases reported by the author, an early peripheral operation had been done, and hemorrhage accompanied the removal of the ganglion. The findings in the two ganglia are summed up as follows: "In both of them the nerve cells must be regarded as pathologically altered, but in neither to such a degree or extent as to consider them primarily affected. The definite changes which are found in acute or long-standing parenchymatous nerve-cell affections are certainly missed in these two cases. The more intense cell changes of the first case lose their importance, in a measure at least, on account of the previous peripheral operation on this ganglion. Pathological the cells certainly are, but secondarily affected." Neuritis and atrophy are probably present in both cases, and concentric bodies, similar to those described by Spiller and Barker, who designate them by this name as brain sand, but which are probably corpora amylacea, were found in the second case. Their pathological significance is very slight, as their number is so small. The author thinks it quite evident that "trigeminal neuralgia is not a definite disease, but merely the symptom of various processes affecting the fifth nerve anywhere in its course, from the ganglion to its peripheral termination." There are two main divisions of trigeminal neuralgic affections: "First, and the more common, is a neuritis beginning in the terminal divisions of the fifth nerve and having a tendency to ascend to the ganglion. Second, an interstitial inflammation, chronic and progressive, of the ganglion body itself. A third division is possible, and there have been two cases reported, that is, a central neuralgia or neuritis affecting the sensory root as it leaves the ganglion on its way to the pons." "There remain, then, two general lines along which the study of neuralgia of the trigeminus should proceed. First, such an improvement of the operative technique as to render the operation comparatively safe, as suggested by Keen; and second, such an improvement in our clinical knowledge that it will be possible to tell what portion of the trigeminus is affected. If it is the ganglion, then operation for its removal will be indicated. If in the peripheral branches, then peripheral operation is advisable."

Barker reports the microscopic findings in Gasserian ganglia, some removed at autopsy, and some by operation. In the case of an experiment on a dog's Gasserian ganglion, with evulsion of the nervus maxillaris on the right side, the ganglion on the right sides shows rows

of ganglion cells chiefly situated in the middle of the ganglion, which show the typical "reaction at a distance," *i.e.*, displacement of the nucleus to the side of the cell with chromatolysis. Where the changes are most intense, nearly all the cells have undergone alteration. At the peripheries of this intense area altered cells are scattered in among healthy cells (nothing is said of the ganglion of the left side). The conclusions drawn in regard to operative measures in tic douloureux are:

1. If a ganglion be entirely removed there need be no fear of a return of pain from irritation of the stump of the nervus trigeminus left behind, for all of the axons of this stump will degenerate to their terminations in the pons and medulla, down as far as the cervical cord. The end of a nerve in an amputation stump is not analogous.

2. Complete removal of a Gasserian ganglion utterly abolishes the possibility of calling forth sensations in consciousness by applying stimuli to the domain of peripheral distribution of the nerves connected with the ganglion of the corresponding side; retention of sensation on peripheral stimulation after operation indicates incomplete removal.

3. If pain persists, paroxysmally or continuously, after complete removal of the ganglion, or after evulsion of the nervus trigeminus from the pons, the ganglion being left *in situ*, a lesion of the central neurones—of the second or of higher orders—of the trigeminal afferent conduction path is indicated.

4. In tic douloureux due to disease of the peripheral set of trigeminal sensory neurones, relief should be as complete and permanent by cutting the nervus trigeminus between the ganglion and the pons and evulsing the central end without removal of the ganglion as when the ganglion itself is excised.

Etiology.

In the etiology of nervous diseases there has not been much demonstrated that is new within the last five years. The wide prevalence of influenza has brought to light the fact that neuritis of various types, either localized neuritis of some individual nerve or nerves or a more general multiple neuritis, may be caused by this poison. It is necessary, however, in considering this subject to caution observers against the prevalent error of attributing too much to influenza. The tendency has been to attribute too much to influenza, and it is probable that some of the numerous nervous affections which have been ascribed to it have really been due to other causes. Starr in a recent paper has emphasized the frequency of neuritis as a sequence of grippe, and says that he has noticed all types. Among other causes

may be mentioned sulphonal, trional, and some coal-tar products as among the more novel and recent causes of multiple neuritis. The difficulty of determining the exact causation of some forms of neuritis was well seen in a case of the author's in the Methodist Episcopal Hospital in Philadelphia. This patient, a young woman, was admitted to the wards in a typhoid state, with a history of very sudden onset of her disease, and of a short duration. She had been ill but for three or four days when first seen. She was delirious, with high temperature, rapid pulse, and in a state that closely resembled an attack of cerebrospinal meningitis. This diagnosis was still further suggested by the fact that the patient had a well-marked paralysis of the sixth nerve on the left side. In a few days, however, the type of the fever changed distinctly. The patient improved slightly, recovered consciousness, and began to have a daily chill followed by a high temperature. Before the second week was well advanced it was demonstrated that the patient was suffering with a profound attack of malarial poisoning. A few doses of quinine effected a cure, and with the cure the sixth-nerve paralysis disappeared.

This case points to a malarial poisoning as a possible cause of a paralysis of individual nerves, and is certainly a rare observation. Another cause which has been brought prominently into notice within the last few years is arsenic in beer. A large number of cases have been reported, especially in England. The arsenic in these cases acted possibly in conjunction with the alcohol of the beer. Syphilis as a cause of multiple neuritis is not often in evidence. We report one case below by Fry in which this occurrence is indicated.

Strachan in an interesting paper, also quoted below, describes a form of multiple neuritis very prevalent in the West Indies, which he ascribes also to a malarial organism. We believe that the subject of the nerve complications of malarial poisoning has not been sufficiently worked out, and that in time it may be found that affections of the nervous system from malarial poisoning are rather more common than has been supposed.

Frazier, also in a case reported below, ascribes diabetic neuritis to a substance formed from sugar and not improbably from the derivatives of alcohol, produced from glucose of diabetes mellitus. Carbonic-oxide poisoning has also figured lately as a cause of neuritis. The various toxæmias continue to cause various affections of the peripheral nervous system, but there are few if any new ones to add to the list. Some observers have thought that diphtheria paralysis is rather less common than formerly, and they ascribe this to the more general use of antidiphtheritic serum.

Multiple Neuritis.

This disease is of perennial interest to neurologists, and is constantly being given more and more prominence. There has been a vast deal written about it even in the short space of six years, but there has been comparatively little in all this literature that is really new. The report in England of a large number of cases of multiple neuritis due to arsenical poisoning in beer-drinkers has perhaps attracted the most attention. These cases have given a splendid opportunity for the study of the action of arsenic upon the peripheral nervous system, and from this it seems that there are certain differentiating points. These were really not unknown before, but the number of cases in this epidemic has been so great that these particular points are more and more emphasized. It is important to call attention to the fact, however, that these cases occurred in beer-drinkers, and that the arsenic was probably not the only cause of the symptoms. It was mixed with a large amount of alcohol; to such an extent, in fact, that it is rather difficult to state in some cases to what extent the one cause or the other was the predominant one. As we have already said, however, there were in these cases certain distinguishing features, and these have been brought out in various papers, some of which we refer to below. Sulphide of carbon has been noted in a few cases as a cause of multiple neuritis. In Philadelphia an interesting case has been made the subject of a medico-legal inquiry which involved the question of the causation of a multiple neuritis by hydrofluoric acid. We believe that this is entirely a novel observation, and shall refer to the case in detail below.

Tuberculosis has been accused by some authors of being the cause of multiple neuritis. The observations, however, are very few. In our former article we pointed out the fact that alcohol might be as much a cause of neuritis in some of these cases as the tuberculous poison. As is well known, alcohol is sometimes given in large quantities to these patients, or even taken by them on their own initiative, with the idea that it is curative. This idea is by no means exploded at the present day, although perhaps not so prevalent as formerly. In any case of multiple neuritis occurring in a tuberculous patient, the possibility of excessive use of alcohol should not be ignored. The practice will be denied by some of these unfortunates, or if acknowledged, its importance will be minimized by them. We have not yet found a case which seems to us to be a good example of pure multiple neuritis due to tuberculous poisoning. Raymond has reported a case of multiple neuritis from an odd cause, namely, an injection for a gonorrhœal affection.

Starr reviews the various causes of multiple neuritis; the toxins, metallic poisons, such as arsenic, lead, mercury, copper, phosphorus, and silver; and non-metallic poisons, such as alcohol, carbonic oxide, bisulphide of carbon, sulphonal and trional, the coal-tar products, and nitrobenzol, all of which are noticed at length. Alcohol seems to be the most frequent of all the causes. The second type is that of multiple neuritis from dyscrasia. In this class he gives the epidemic form known as beriberi, and leprous neuritis, and that occurring as an accompaniment or sequela of diphtheria, which Starr holds is less frequent since the use of antitoxin. He emphasizes the frequency of neuritis following la grippe, from which cause he has noticed all types. There are certain other dyscrasias, such as tuberculosis, rheumatism, gout, and diabetes; there are also cases of general multiple neuritis occurring in the carcinomatous, and in old persons with atheroma. It is probable that syphilis does not enter as a factor in the etiology of this affection. Finally, he alludes to certain cases in which the cause cannot be determined, which he must call idiopathic, and reports such a one. A double causation may often be ascertained. Thus arsenic or lead may act together with alcohol or influenza.

H. M. Thomas contributes a letter on recurrent polyneuritis, and describes a case with a fifth attack of the disease. He concludes as follows:

1. That there are patients who show a marked tendency to the occurrence of repeated attacks of multiple neuritis.

2. That we do not at present know how the poisons which may cause the neuritis differ from each other in their liability to cause recurrences, except in the case of lead, which seems particularly prone to give rise to recurrent attacks of paralysis, at times even when there has been no reëxposure to the poison.

3. That we are not able to state upon what the repeated attacks of multiple neuritis depend, whether they are simply the manifestation of an unusual individual predisposition of the nerves to become diseased, or whether the first attack of neuritis itself leaves the nerves more liable to the second attack. That one attack of neuritis does not impart immunity to the tissues against a second attack stands as a corollary to the conclusions which we have already drawn.

Fry reports a case of multiple syphilitic neuritis. The patient, a male, thirty-two years of age, had a severe headache in March, 1897, which yielded to antisyphilitic treatment within about ten days. In June, a syphilitic lesion of the tonsil. In July and August, headache again, but not severe; no symptoms of focal disease of the nervous system. October 26th, a sudden right hemiplegia, involving the arm and leg, but not the face; probably due to a lesion in the internal capsule; no other lesions of the central nervous system. November 15th,

beginning of a paraplegia with hyperæsthesia and anæsthesia of all the extremities, especially of the hands and feet, and later a complete paraplegia with flaccid muscles and reaction of degeneration in the legs, and absent knee-jerk, and marked weakness of the hands and forearms. A diagnosis of multiple neuritis involving all of the extremities was made. In March, 1898, returning motility was noted, and later a gradual recovery from paraplegia, with returning knee-jerk. There was no probable explanation of the neuritis other than that it was of syphilitic origin.

C. T. Dercum reports a case of idiopathic multiple neuritis in a child five years old. No cause could be found.

Stein reports three cases of senile polyneuritis. He is of the opinion that these cases were cases of a primary degenerative neuritis without direct connection with arteriosclerosis, but to be regarded as a purely senile change.

Raymond reports a case of polyneuritis due to intoxication with sulphide of carbon. Most of the nerves of the right arm and the sensory nerves of the left arm were involved.

Raw, Barendt, and Warrington made a report of one hundred and sixty-nine cases of arsenical poisoning which occurred in beer-drinkers in Liverpool. From the study of these cases they say that arsenical neuritis is characterized by:

1. Sudden appearance of paræsthesia in the hands and feet.
2. Severe pains in the soles of the feet, especially when walking, and also in the heels and in the balls of the large and small toes.
3. The appearance of erythromelalgia in the soles of the feet.
4. No marked decrease in sensibility.
5. Absence of ataxia and paresis.

Mental disturbances were absent even in advanced cases. In no cases were the cranial nerves, the intercostal nerves, or the phrenic nerve involved.

Boinet reports two cases of perforating plantar ulcer; in the first the lesion was symmetrical on both heels; there were very extensive sensory disturbances without amyotrophy. In the second case the plantar surface of the foot in the region of the first metatarsal bone was affected in this area. There was marked anæsthesia for pain and temperature extending to the dorsal surface of the great toe. Boinet was unable to find any similar cases in the literature, though he thinks these cases of alcoholic polyneuritis with perforating ulcer are probably not rare.

Acevedo reports a case of gangrene of the feet due to a neuritis. Stretching of the posterior tibial and of the external saphenous nerves brought about a cure, so that the patient could go about on crutches. The cause of the neuritis, as well as the question whether

recovery was due simply to the stretching of the nerves or not, remains undecided.

Schwabe reports a case of multiple neuritis, due to carbonic oxide poisoning, with involvement of the optic nerves. The affection began with a neuritis of the right sciatic, and slight symptoms in the region of the left sciatic, the femoral nerves, the nerves of the arm, and the lower branch of the left facial. There was also present a bilateral retrobulbar optic neuritis, with perceptible changes in the papillæ, relative central scotomata, as well as a right-sided paralysis of accommodation.

Strachan contributes an article on a form of multiple neuritis very prevalent in the West Indies. The chief features of this disease are: (1) a more or less widespread neuritis, involving some of the nerves of special sense, especially the optic nerve; (2) the occurrence of trophic changes in the skin along the distribution of the nerve terminations, in the muscles, in the mucocutaneous lines, and occasionally in the cornea; (3) the rare but still to be noted occurrence of monoplegias; (4) the fact that the disease may be very severe, lasting for many months or even years; (5) the fact that recovery is the rule, and a fatal termination very rare; (6) and that it attacks many hundreds of persons, at least in Jamaica, the great majority of these being the colored inhabitants who constitute the bulk of the population, though the white residents are not by any means exempt. The author thinks that the poison causing this disease is probably due to the malarial organism.

Fraser reports a case of diabetic neuritis, a diagnosis confirmed by post-mortem examination, in which degeneration of the medullary sheath, persistence of the axis cylinder, and absence of secondary degeneration in the nerves or in their end organs were noted. A remarkable change in the muscle was noted, characterized by small areas in which fat droplets were formed in rows between the fibrillæ of the muscle—"a disseminated interfibrillary fatty degeneration of the muscle"—probably due to an independent action on the muscle itself of some toxic substance, and not to any want of trophic influence on the part of the nerve. The neuritis is apparently caused by a substance originating from sugar, and not improbably from a derivation of alcohol produced from the glucose of diabetes mellitus.

Wetzel reports a case of multiple neuritis with athetosis and Raynaud's disease. The patient, a single woman of seventy years of age, was afflicted with symmetrical gangrene of the second toe of both feet, the right one five months after the left. Both toes were amputated. At the same time she developed a multiple neuritis with flaccid paralysis and atrophy of the lower extremities, and later of the left arm. Paralysis of the facial nerve followed. Early in the dis-

ease athetosis in both feet was noticed, and this persisted till death. The author thinks that a neuritis, consequent upon arteriosclerosis, was the cause of trophic disturbances and the symmetrical gangrene. It is probable that a secondary ascending myelitis with special involvement of the pyramidal tracts was present.

Raymond reports a case of polyneuritis with systemic disease in the lower extremities, probably due to an injection in a case of gonorrhœa. There was a generalized polyneuritis, with facial diplegia.

Cestan reports a case of polyneuritis most probably due to tuberculosis. Both legs were involved, though the disturbances were entirely motor. Alcohol could be excluded in this case, and the author considers the case one of tuberculous origin.

Burr and McCarthy report a case of acute alcoholic multiple neuritis, with involvement of the bladder and rectum and acute widespread degeneration of the central and peripheral nervous systems, of the pelvic nerves, the vagus, and phrenic, with hemorrhagic extravasation within the sheaths of the latter; degeneration of both fibre and cellular structure of the Gasserian ganglion (the other intervertebral and cerebral nerve ganglia not being examined) and intra- and extracapsular round-cell infiltration and proliferation about the ganglion cells which were in an advanced state of chromatolysis. The authors think that this case shows that a multiple neuritis with demonstrable lesions affecting the bladder and rectal nerves can occur, and that too much stress should not be laid on this point in differential diagnosis from cord disease.

Köster reports a case of lead paralysis with peculiar localization. The case is unique and fully described, with illustrations. The new and important part of the contribution is the observation of a patient with colic and pains in the joints as the first symptoms of lead palsy, and with a symmetrical paralysis of the interossei and lumbricales of both feet, instead of the typical extensor paralysis of the forearms. And in place of the usual localization of lead palsy—when confined to the nerves of the leg, *i.e.*, of the peroneal type—this is a case of most unusual localization in the isolated and diseased interossei and the abducentes hallucis of both feet.

Spitzer reports a case of acute mercurial polyneuritis occurring in a man, twenty-nine years of age, the subject of an old cerebral affection, causing diplopia and paralysis of the uvula. The patient had a recent syphilitic exanthem, and while he was getting twenty-two 3-gm. inunctions of mercury, he developed severe continuous pains in the lower extremities and ataxia of both legs. Pupillary symptoms were absent. There was no disturbance of function of the bladder or rectum. The tendon reflexes were increased. Romberg's symptom was present. When the mercurial treatment was completely stopped

the pains gradually disappeared, while new syphilitic lesions became manifest two and one-half months after the first symptoms. The disease of the nerves had entirely disappeared, but at this time palmar syphilides and lesions on the trunk were present. A review of the literature of syphilitic and mercurial polyneuritis is given to show that according to anatomical, experimental, and clinical investigations an acute polyneuritis due to mercurial poisoning is possible, and indeed probable, though a surely proven case has not been reported. The author thinks his case was due to mercurial poisoning, a diagnosis supported by the presence of mercury in the urine during the neuritis. Perhaps this mercurial polyneuritis occurred because the nervous system was a *locus minoris resistentiæ*, as a cerebral lesion was probably present.

The Optic Nerve.

The optic nerve is so fequently the object of study that the literature rapidly increases. During the past six years there has been much contributed on this subject. But much of this, of course, has embodied no essentially new points. As we explained in our chapter in the eleventh volume of this work, the optic nerve is embryologically a process which is developed from the forebrain. Its relations are very complex; its functions are of the highest importance; and its reactions to various pathological conditions are very numerous. It is frequently affected in diseases of the central nervous system, both brain and spinal cord, as well as in general constitutional poisoning, and dyscrasiæ. The following abstracts embody some of the more novel of the recent observations:

Adamück divides inflammations of the optic nerve into general and partial neuritis. The category of general neuritis includes œdematous neuritis, or choked disc, and simple neuritis, or the neuritis descendans of von Graefe. The category of partial neuritis includes peripheric neuritis or perineuritis, central or axial neuritis, and focal or disseminated neuritis. In perineuritis there will be a concentric contraction of the visual field, with or without a central scotoma according as the affection is near the ball or farther back in the orbit, the affection probably beginning always at the apex of the orbit. In axial neuritis there will be no contraction of the field, but a central scotoma, which need not necessarily be regularly oval, as Wilbrand states, but which can have various forms. In neuritis disseminata there will be early in the disease a number of small scotomata, some of which may later coalesce to form a central scotoma of irregular form. Examples of the latter form of neuritis are found in disseminated sclerosis, in which small foci of degeneration are found in the optic nerve, while the intervening tissues are unaffected.

Kollock reports a case of optic-nerve atrophy treated by inhalations of nitrite of amyl, with marked improvement. The case was not due to tobacco or alcohol, and no improvement had followed the use of iodide of potassium and strychnine.

De Wecker advises injection of normal salt solution in the treatment of the toxic amblyopias. In his cases from 60 to 100, exceptionally as much as 200 gm. of Cheron's fluid was used daily. Cheron's serum consists of 1 part phenic acid, 2 parts of chloride of sodium, 8 parts of sulphate of sodium, and 4 parts of phosphate of sodium, in 100 parts of water. Injection is given subcutaneously. Visual acuity improves markedly after three or four injections.

Galezowski reports two cases of peculiar atrophy of the optic nerves, due to a change in the lymphatic vessels. He divides optic atrophies into: (1) cortical atrophy; (2) atrophy due to a change in the visual centres; (3) glaucomatous atrophy; (4) atrophy caused by a change in the lymph in the course of the optic nerve.

The causes of this latter form of pupillary atrophy, which the author calls lymphangitic atrophy, may be various; some peripheral and extending centrally; and others taking their origin from the cerebral lymphatic spaces to end in the lymphatic spaces of the eye.

Reiss reports cases of atrophy of the optic nerve much benefited by intramuscular injections of the biniodide of mercury. The author believes this to be the ideal method of administering the drug, without the inconveniences of its unpleasant effect, and one which seems to be particularly efficient in atrophy of the optic nerve.

Strzeminski reports three cases of retrobulbar optic neuritis in the same family. The cases occurred in three generations, with direct transmission. The author considers the cases hereditary, as all other causes were lacking.

J. Mayers also reports cases of hereditary optic atrophy and hereditary choroiditis. Other causes could be excluded.

Renaud finds that sympatheticectomy is of value in obtaining the vasodilating effect required in the treatment of optic-nerve atrophy, and he reports cases in which he has performed the operation with benefit. He thinks it is of value only in cases in which atrophy is beginning or is incomplete, and before too pronounced structural changes have taken place. There must be considerable normal nerve tissue remaining. It is only necessary that the superior ganglion of the cervical sympathetic be removed, as it is from this ganglion alone that the sympathetic fibres to the eye and orbit are derived. He would also recommend its being removed on both sides, and suggests that the lack of success in glaucoma may sometimes be due to unilateral operation.

The Third Nerve.

Affections of the third nerve have been so frequently and so completely reported in the past that very little that is new has transpired in the last five or six years. Among the most unusual affections of this nerve are certain recurrent attacks of paralysis. Such attacks occur sometimes in conjunction with migraine, and were formerly described by Charcot as migraine ophthalmoplegique.

Leszynsky reports a case of recurrent oculomotor paralysis which occured in a woman twenty-nine years of age, and a typesetter by occupation. The first attack of oculomotor paralysis took place in her twelfth year; the second in her nineteenth year; the third in her twenty-second year; the fourth in her twenty-seventh year; and the fifth occurred three weeks before the report. The cardinal symptoms of this intermittent paralysis of the third nerve are the unilateral character of the headache, the limitation of the ocular paralysis to one side (the pain and paralysis being on the same side), the involvement of the same nerve in all attacks, the frequent involvement of all branches of the nerve, and the intervals of complete freedom.

Bregman reports a case of peripheral traumatic oculomotor palsy, with paralysis of the trochear nerve—probably of moderate grade—as, two months after the initial symptoms, the functions began to return and the reactions of degeneration became less and less. These reactions of degeneration of the levator palpebræ superioris have been described by Wertheim-Salomonson. In many forms of peripheral oculomotor palsy the irritability of the levator palpebræ superioris is increased, so that the lid is raised when but a weak current of less than 1.0 milliampère is used. The cathodal closing contraction is first to appear, then the anodal opening contraction, which is soon exceeded by the anodal closing contraction. This reaction of degeneration is used in the diagnosis of oculomotor palsy. The absence of the reaction from two to three weeks after the beginning of the ptosis indicates a mild degree of paralysis; the presence of the reaction indicates a moderate or severe form. The rapid disappearance of the reaction is regarded by Wertheim-Salomonson as a sign of beginning recovery, though Bregman believes that this can occur in cases of progressive degeneration.

P. J. Möbius reports a case of periodic oculomotor palsy which occurred in a woman thirty-one years of age. She had her first attack at twenty-two years of age, and then one about every two years until the time of this report, when she had her fifth attack. Marked headache behind the left eye, nausea, and vomiting ushered in the attacks. On the next day the left eye was " smaller," and in the course of two days

it was shut. Headache and vomiting persisted for two days, followed by slight pain over the left eye. The left eye was closed for about twelve days. During the last attack complete paralysis of the left oculomotor nerve was present. The case was one with all the characteristics of periodic recurring oculomotor palsy, *i.e.*, complete unilateral oculomotor palsy recurring from time to time since the childhood or youth of the patient, and ushered in by headache and vomiting. This disease must be carefully diagnosticated from the many other forms of oculomotor palsy, which may appear with headache. All cases in which the attacks begin after the thirtieth year, in which migraine is not present, and in which complete unilateral oculomotor palsy is absent, must be excluded. Möbius reviews the literature of the subject, not commented on up to the time of the present article; goes over the details of the characteristic symptoms and signs of this disease, and discusses the possible location of the lesion. He believes that the lesion is an organic one, and that it is probably a basal peripheral lesion.

The Fifth Nerve.

The fifth nerve is one of the most interesting and important from the standpoint both of the neurologist and of the surgeon. Much work continues to be done in the domain both of the pathology and of the surgery of the trifacial, which has been referred to in the discussion of the Gasserian ganglion. Such satisfactory results have been reported by some surgeons in that dreadul affection, tic douloureux, that it has now become a settled doctrine of practice that the only rational means for relief is in surgical operation. We say this advisedly, for while we know that in many cases drug treatment is still advised and persistently used, such treatment is almost unanimously conceded to be disappointing. Cases, however, occur in which the drug treatment has to be used because of the unwillingness of the patient to submit to surgical operation. In such cases we have no resort but to adhere to the old treatment, such as is outlined in our former chapter. There has practically been nothing new added to our knowledge of drug therapeutics of tic douloureux. We say this in spite of the fact that a great many drugs are still lauded or defended, but we have no knowledge of any agent which has made good its claims within the last five years to be considered a valuable addition to our armamentarium. This being so, there remains practically little to say on the subject.

We would call especial attention to the report of the treatment of trigeminal neuralgia by resection of the cervical sympathetic. This treatment, although much lauded by Cavazzani, has not been exten-

sively tried. Among the important contributions to the pathology of tic douloureux we may mention Spiller's study on the Gasserian ganglion.

Sixth Nerve.

We have called attention above to the possibility of malaria and influenza being causes of infection of various peripheral nerves. In the author's case, referred to in the section on Etiology, the patient had a paralysis of the sixth nerve evidently due to malarial poisoning, although the question was raised at the time whether there might not have been a double infection, as the symptoms were somewhat indicative of grip, the type of the case later changing to one of distinct intermittent fever. In that case the sixth nerve was entirely paralyzed, but recovered within a few weeks after a cessation of the febrile symptoms. Several cases have been reported from Italy in which symptoms of multiple neuritis were attributed to malarial poison. The Italians have been recently studying the phenomena of malarial infection so thoroughly that they have found some indications that the peripheral nervous system may be involved in malaria. Such cases, however, have heretofore been rare.

Van Millingen reports a case of bilateral paralysis of the external recti muscles of the eye consequent upon an attack of influenza. The influenza was complicated by inflammation of the middle ear. The paralysis disappeared gradually after faradization.

Seventh Nerve.

Fry has recently reported a case of double Bell's palsy. This occurred in a man who had been exposed in cold weather while working about a freight station. Both sides of the face were involved within a few days, one side preceding the other by a day or two. Fry gives a graphic description of the patient, especially of the peculiar facial expression or lack of expression. The mask-like stolidity of the muscles responded in no respect to any expression of emotion or intelligence. Double Bell's palsy is rare, though not unheard of. Fry's case is the only one we recall that has been reported within the last few years. In such a case, of course, the chief phenomena are simply those which attend the unilateral paralysis of the seventh nerve, such as the complete paralysis of the muscles with slight atrophy and the reactions of degeneration. The causes of double Bell's palsy are the same as for the unilateral variety; and considering how frequently the face is exposed on both sides to extreme cold, it is rather remarkable that cases of bilateral palsy are not more often reported. It must

be remembered, however, that in most cases of Bell's palsy there is a distinct history of exposure on one side of the face only, as, for instance, in the case of a person sitting in a strong draught at an open door or window of a house or in a railroad car in rapid motion.

I have lately seen an instance of complete anæsthesia of the whole side of the face, complicating Bell's palsy. This is a rare instance. This patient was hysterical to a high degree, and it was found that she had a profound anæsthesia of the whole side of the paralyzed face. The motor portion of the fifth nerve, however, was not involved, nor was the anæsthesia strictly limited to the territory of the fifth nerve. This last feature alone was sufficient to indicate that it was not of organic origin. The case was reported as one of organic Bell's palsy with an hysterical anæsthesia of the face, a diagnosis which was subsequently confirmed. In discussing this case I wrote as follows:

FIG. 40.—Anæsthesia Complicating a Case of Bell's Palsy.

Involvement of sensation in a minor degree is not uncommon in ordinary cases of peripheral paralysis of the seventh nerve. This implication of the fifth nerve in such cases is, however, merely shown, as a rule, by pain in and around the point of exit of the seventh nerve from the skull. This pain is usually not severe and not long continued. On the other hand, a true anæsthesia in ordinary Bell's palsy is very rare, and even when present is usually but limited in extent and quite evanescent. In my own observations of peripheral paralysis of the seventh nerve, of the ordinary type due to cold, and known as Bell's palsy, I have never seen until now a well-marked anæsthesia. I have, of course, seen a conjoint paralysis of the fifth and seventh nerves, due to a gross lesion, such as a tumor, within the cranium, but of such cases I am not speaking here.

There is apparently very little recorded about anæsthesia or other involvement of the fifth nerve in cases of Bell's palsy. The reason must be that such involvement is rare. Erb regards it as remarkable, considering the intimate association that exists between the fibres of the fifth nerve and those of the pes anserinus, that sensibility is not oftener involved, and regards this exemption as proof that in ordinary facial paralysis the inflammation is usually higher up in the trunk of the facial. Gowers says he has seen a few cases of diminished sensibility on the cheek, but his explanation that this is due to diminished

sensibility of the nucleus of the fifth nerve due to the diminution of the number of muscular impressions, is quite unsatisfactory. Mills says that occasionally one or more branches of the trifacial may be involved in Bell's palsy, and this is due to a spread of the inflammation by contiguous structures. Eulenberg and others have recorded the occurrence of herpes zoster in cases of paralysis of the seventh nerve, but in such cases I should suspect a deep-seated lesion probably acting as an irritant to the Gasserian ganglion. Notta, in 1860, described a form of neuralgic Bell's palsy in which the first symptom was pain in the suboccipital and auriculotemporal nerves, followed after a period of eight days by the facial paralysis. But in this affection there was no anæsthesia. The affection was a most anomalous one and suggests a resemblance to ophthalmic migraine, in which paralysis of the ocular muscles follows a severe bout of pain in the ophthalmic division of the fifth nerve. It was certainly not like an ordinary Bell's palsy, and I have never seen any record of other cases like it.

Webber, of Boston, wrote a paper on pain (not anæsthesia) in Bell's palsy. He suggests, somewhat as Mills has done, that a "rheumatoid" inflammation of the trunk of the fifth nerve might occur at the points of exit of the nerve from the skull, just as occurs in the case of the seventh nerve. But in such an affection, I should think, anæsthesia would be present as well as pain. The occurrence of pain in Bell's palsy is, in fact, not difficult to understand; it may readily be caused by the swelling of the trunk of the seventh and consequent involvement of the small fibres of the fifth with which the trunk of the seventh is doubtless supplied. But the problem of a complete anæsthesia in these cases is a far different one.

Various Peripheral Nerves.

Among cases of unusual interest which have occurred in various peripheral nerves the following have been selected:

Warda reports a case of neuritis of the external cutaneous nerve of the thigh. The author thinks that the primary cause was bicycle riding, and that the acute exacerbation was due to application of ice during an attack of appendicitis, though the neuritis was on the left side, and the ice mostly on the right side. The appendicitis itself was thought not to have any causal relation with the neuritis.

Brush reports two cases of nerve and muscle degeneration due to high-tension electric currents. Both cases were the results of electric shocks received from trolley-car electricity. There were atrophy of the muscles and abnormal response to the electric current. The author says "very high-tension currents produce coagulation of cell

constituents, and even though such a current is not employed on the trolley wires, the prolonged application might more than counterbalance the moderate degree of tension."

Lermoyez and Laborde report a case of associated paralysis of both the internal and external branches of the right spinal accessory nerve in a woman of sixty-two years. Complete paralysis of the right recurrent laryngeal was found. But there was not right-sided laryngeal hemianæsthesia. Deglutition was difficult, as in complete paralysis of the internal branch of the spinal accessory. But the external branch was also paralyzed, since the sternocleidomastoid and the trapezius muscles on the right side showed paralysis and atrophy. The facial, hypoglossal, and pneumogastric nerves were unaffected. These symptoms were preceded by a right-sided retropharyngeal abscess. This lesion, a neuritis of both branches of the spinal accessory nerve, is very rare, especially without the involvement of the other cranial nerves.

Pershing contributes an article on pressure neuritis caused during surgical operations. The cases were all more or less alike, and due to the fact that the arm had hung over the edge of the table so that the nerve trunks were subjected to pressure—probably for some time. Neuritis of the external popliteal was also caused by pressure during an operation. The prognosis in these cases is good.

Delorme reports a case of traumatic ulnar neuritis of nineteen months' duration cured by forced digital compression. Neurectomy and neurotomy had been done without benefit.

Taylor reports a case of double paralytic varus from peripheral neuritis. The case occurred in a girl of thirteen years, and was apparently without known cause.

Hoffman reports a case of isolated atrophic paralysis of the musculocutaneous nerve, apparently without definite cause. There was a marked atrophy of the muscles supplied by this nerve, which persisted for over a year, and the author then gave an unfavorable prognosis. Compensatory hypertrophy of the supinator longus, and of the external portion of the coracobrachialis gave the patient the power of using the arm, though with less strength, and early fatigue.

Courtois-Suffit and Dellile report a case of sciatica treated and rapidly cured by lumbar puncture and the subarachnoidian injection of cocaine. A small dose (0.005 mgm.) of cocaine was injected and the result was almost immediate. On the same day the patient walked for an hour and lost his lameness. The improvement continued on the next day. Millard thought that lumbar puncture is useful when the patient is seen at the beginning of the trouble.

Peraire and Mally report a case of diffuse lipoma in the median nerve requiring resection of 8 cm. of the nerve. After removal all

the movements of the fingers were retained, and the patient resumed her occupation of seamstress without disturbance of any kind. The sensibility was normal nineteen months after, except for a patch of anæsthesia in the centre of the pulp of the forefinger. The flexor brevis pollicis had evidently assumed some of the functions of the paralyzed antagonist and the abductor brevis.

Injury to the Median Nerve.—Dr. Haldor Sneve reports an exceedingly interesting case of trauma of the median nerve. The patient, a young farmer aged twenty years, had been cut with a scythe some months before. The wound was on the anterior surface of the right forearm just below the elbow. The median nerve had evidently been severed, and its retracted proximal end, upon which was a large neuroma, could be felt about two inches above the scar. Painless whitlows had formed in the ends of the index and middle fingers, and had resulted in the loss of the third phalanx of each of these fingers. Anæsthesia was present on the palmar surface of these two fingers and thumb and on the radial half of the palm of the hand. On the dorsal aspect the loss of sensation involved only the distal half of the two fingers. The grip of the hand was weakened, and the thumb, index and middle fingers could be flexed only partly. The thumb could be flexed, however, so as to touch the ends of the fingers. Supination and pronation were preserved. On the whole, motion was not so much affected as might have been expected. The most interesting feature of the case was the painless destructive process which involved the tips of the fingers. The case illustrates very clearly the trophic functions of the nerves.

The Reflexes.

The Muscular Factors in Ankle Clonus.—It has usually been assumed that both the gastrocnemius and soleus muscles are concerned in the mechanism of ankle clonus. This symptom is so commonly sought for and observed in diseases of the nervous system that it is somewhat remarkable it has not been more carefully analyzed. In a case of trauma of the spinal cord, recently observed, Dr. S. Weir Mitchell found that the very remarkable clonus present was caused by the faction of the soleus alone. This observation he verified by the study of other cases and by the clonus that can often be excited in the normal person. Mitchell finds the explanation of this fact in the anatomical differences of the two muscles. Thus, the gastrocnemius has its origin on the femur; the soleus, on the tibia. If the leg is flexed on the thigh, the gastrocnemius, being attached to the femur, is too relaxed to give rise to clonus; but the soleus, being attached to the tibia, is not relaxed, and may be jerked sufficiently by forced dorsiflexion of

the foot on the leg to respond by a clonic movement. If the leg, however, is put in extreme passive extension on the thigh, the pull made thus on the common tendon of the two muscles is so great that it prevents either muscle being jerked sharply enough to occasion clonus.

Dr. W. G. Spiller has recently described the importance of the lacrymal reflex in the diagnosis between organic and hysterical affections of the face. By the term lacrymal reflex he refers to the secretion of tears caused reflexly by irritation. He has observed that in an extraordinary case of hysteria, although the conjunctiva was insensitive and irritation did not cause closing of the eye, it did produce a flow of tears from the anæsthetic eye. In other words, the lacrymal reflex was not abolished by hysterical anæsthesia.

Gilles de la Tourette in his treatise on hysteria has also called attention to the fact that in anæsthesia of the ocular mucous membrane due to hysteria, direct contact of a piece of paper caused the tears to be immediately secreted and in the same abundance as in the other eye. The phenomena had also been observed by Pitres. Dr. Spiller had observed that in cases of complete organic anæsthesia of the conjunctiva, as for instance, after the removal of the Gasserian ganglion, there was a diminution of this lacrymal reflex—in other words, the secretion of tears was not excited by irritation by the conjunctiva, at least not to the same extent as in the sound eye. He has pointed out very justly that this difference in the lacrymal reflex in hysteria and in organic anæsthesia may constitute a point for differential diagnosis between these two classes of affections. For instance, in a case, such as that reported above by the author, of Bell's palsy of organic origin associated with the anæsthesia of the same side of the face in which the anæsthesia was believed to be hysterical, this lacrymal reflex might give us data by which to establish a differential diagnosis.

Medico-Legal Aspects.

In closing this article reference may be made to some of the medico-legal aspects of injuries of the peripheral nervous system. The literature on the subject is scanty, and not much has transpired in the last five or six years bearing on this subject. A most important case has occurred in Philadelphia, and has been made the subject of a medico-legal inquiry. In this case, the patient, a man, had worked for a short time in a factory in which hydrofluoric acid was used for etching on glass.

It will hardly be denied that there are some forms of paralysis which are so highly characteristic of their several causes that these causes can almost be recognized at a glance. In other words, the symp-

tomatology of some distinct forms of paralysis at once indicates the causes from which the paralysis occurs. We do not have far to go in clinical neurology to find instances in support of this rule. In fact, in clinical work this rule is so constantly relied on in making a diagnosis that it would probably cause a momentary surprise to most observers to have it called in question as one of great reliability. In order to illustrate the rule, instances may be briefly marshalled. For instance, in the case of the third nerve, we have a form of paralysis which is usually considered quite pathognomonic of its cause. To such an extent is this so that Ricord gave utterance to the aphorism (now almost trite) that "syphilis places its sign manual on the third nerve." In a case, for instance, in which the patient has had some nocturnal headache and insomnia, and develops quite rapidly a complete, or even incomplete, oculomotor paralysis, with its characteristic ptosis, external strabismus, and dilated pupil—in such a case a diagnosis of syphilitic infection of the nerve would be justified. We may even say that it would be more than justified, it would be demanded. The neurologist who under such circumstances would be inclined to dispute or haggle over this diagnosis would probably be looked upon as unnecessarily disputatious. And yet, even in this well-known instance it would have to be frankly acknowledged, if the point were pressed, that the third nerve can be, and sometimes is, involved in other lesions than a syphilitic one. It may be involved in trauma, in brain tumor, in hemorrhage in the midbrain, in locomotor ataxia, and in tuberculous meningitis. In all these instances, however, there would almost inevitably be something in the history of the case, and in the associated symptoms, that would serve to differentiate the palsy from the kind that is caused by syphilis. Thus in none of these instances probably would the symptoms be confined to the third nerve, and the onset would be different. In other words, this is a differentiation that is constantly made in favor of syphilis, and that, too, in cases in which the history of the case gives no clear indication of a primary syphilitic infection. So very sure are neurologists on this point that they find no difficulty in the logic which leads them to say that such and such a characteristic paralysis of the third nerve is a sure indication of syphilis. Therefore this example drawn from third-nerve paralysis supplies a very good text for this paper, which is intended to be an inquiry into the medico-legal value and importance of this identical kind of logic when used to explain another form of peripheral paralysis.

Another instance is the familiar paralysis of the seventh nerve known as Bell's palsy. As a rule, this disease is easily traced to one cause, and that cause is simple exposure to cold. And yet no expert would neglect to note in discussing the value of this symptom complex

that peripheral paralysis of the seventh nerve can be caused by other agents. Thus a chronic ear disease or a tumor favorably located may cause this paralysis. But what I contend for is also proved even in Bell's palsy, and that is that in the vast majority of cases neurologists would have no difficulty in arriving at a positive conclusion, based merely upon the symptoms, and without a history of the case, or with a very imperfect history of it, that the affection was due to one distinct cause, and that that cause was exposure to cold. Therefore Bell's palsy also favors this argument, which is a plea for the validity (both in logic and in medical jurisprudence) of the mental process which attempts to reason backward from a symptom to its cause, when that cause is unknown. This is a sort of pathological detective work, and is, or ought to be, quite legitimate in a court of justice, where most of the legal inquiries are carried on by an exactly similar process, *i.e.*, by a process of circumstantial evidence. And this leads me, before proceeding to the main inquiry, to a slight digression on the subject of one phase of medico-legal inquiries in general. The phase is this: In a court of law the rules of evidence are not always such as are practicable in the wards of a hospital, and are therefore quite inadequate at times to bring forth an elucidation of a pathological question with all the force that it presents to the physician's mind. I contend that there should not be one rule of logic for the court and another for the bedside, but that the function of a medical expert is nothing more nor less than to make a diagnosis. When he has done this his business is ended. In order to do this he should have the privilege of making his diagnosis by the mental processes that have been cultivated by him in the hospital wards, and which have proved again and again their efficacy; and he should not be obliged to reconstruct and fit this clinical logic in order to harmonize it with the precepts of Greenleaf or of Stephen on evidence.

The point to which I now come is to discuss that particular symptom of lead poisoning which is known as wrist-drop. I wish to discuss the pathognomonic significance of that peculiar symptom complex which is caused by the action of lead on the extensor group of muscles in the forearms. I may say in explanation that this is not a mere artificial question, but that it is based upon an actual medico-legal inquiry in which I have recently been engaged, and that this inquiry is of such a nature as to turn principally upon the essential character of this palsy. From the mere clinical standpoint the inquiry might not prove of sufficient interest to claim your attention, but from the medico-legal standpoint it acquires great interest as being the pivoted point upon which a somewhat important case centres. Can it be claimed or asserted that the wrist-drop of lead poisoning presents any or sufficiently characteristic symptoms to allow of a positive diagnosis

of it being made without a history of exposure to lead being attainable? In other words, is the symptom complex of lead wrist-drop recognizable *per se*? Does it differ to such an extent from any other possible form of extensor paralysis of the forearms that it can be positively differentiated to such an extent as to furnish a valid ground for argument in a medico-legal inquiry?

Let us analyze briefly in the first place the symptoms and mechanism of this extensor paralysis. It is well known that lead, like some other poisons, has a peculiar selective action, and that this selective action is about as follows: The muscles affected are principally, but not exclusively, those supplied by the deep-seated interosseous nerve, which is one of the two main branches of the musculospiral nerve. The muscles involved are the long extensor of the fingers, acting upon the proximal phalanges; the extensors primi and secundi internodii pollicis, acting upon the phalanges of the thumb; and the radial and ulnar extensors of the wrist. By a curious anomaly, or exception, the extensor ossi metacarpi pollicis is either not involved or not completely involved. This muscle both extends and abducts the thumb; and by a still more striking exception the important supinator longus muscle, which is partly extensor, also escapes. The effect of this peculiar distribution of the paralysis is to cause wrist-drop of a certain type. The fingers cannot be extended, when the hand falls, because the proximal phalanges are palsied; if, however, these phalanges are passively extended, the distal phalanges can also be extended because this action is by the lumbricales and interossei, which are not paralyzed. When the fingers are extended also the hand cannot be, but if the fingers are flexed the hand can be much better extended. The reason for this, according to Gowers, is because by some obscure physiological process, the extensors of the wrist thus get a better leverage to act. If they are completely paralyzed, however, this movement cannot be effected. On the other hand, as is well known, the fist cannot be tightly clenched; this is in spite of the fact that the flexors are not paralyzed. It is due to the fact that the flexors of the hand require a slight antagonizing action of the extensors in order to act with advantage. This can easily be verified by any one on his own person; in clenching the fist strongly it will be found that the extensors on the back of the forearm contract very perceptibly. The exemption of the supinator longus is one of the essential features of lead poisoning. When the other extensors have wasted this muscle stands out boldly and acts at will. The extensor of the metacarpal bone of the thumb usually also preserves some power. This distribution of paralysis seems odd when we analyze the nerve supply. The supinator which escapes is supplied by a branch from the main trunk of the musculospiral nerve, but the radial extensor of the wrist, which is

badly involved, is also supplied from this main trunk. All the other muscles involved are supplied by the interosseous branch of the musculospiral, but the extensor of the metacarpal bone of the thumb, which escapes, is also supplied by this branch. Hence it is seen that it is impossible to localize the lesion in any one nerve. This peculiar selective action of lead, causing this peculiar distribution of paralysis, is quite characteristic, and so far as I know, is not simulated by any other lesion. Finally, in lead poisoning or wrist-drop there is little if any involvement of the sensory neurones, and the paralysis is always bilateral.

The wrist-drop of lead poisoning can readily be differentiated from musculospiral paralysis, for in the latter the supinator muscle is involved, and from anterior poliomyelitis by the absence of fibrillation, the differences in the electrotonus, and the involvement in the latter of the essential muscles of the hand.

Let us now, after the manner of our colleagues at the bar, assume an hypothetical case.

A middle-aged man, a Hebrew, brings suit against his employers for damages alleged to have been received while in their employment. This employment is that of etching on glass—a process which requires the use of hydrofluoric acid. The patient's work is that of an unskilled laborer, and consists merely of rinsing the glasses after they have been etched. This is done in a trough of running water, so that the actual amount of hydrofluoric acid in contact with the patient's hands is very slight. This work is continued by the patient for only a few days, and the fact is easily proved that no one who ever did this kind of work either before or after this man ever received injury from it. It can be shown that when he was first employed he already had some weakness of his arms. Some months after leaving this employment the plaintiff presents himself at a clinic for nervous diseases with a condition of his forearms about as follows: He has wrist-drop, worse on the right side. The paralysis involves the long extensor of the fingers, the extensors of the wrist, the extensors of the phalanges of the thumb; and allows the supinator longus muscle to escape. There is no involvement of sensation, nor any distinct involvement of any other muscles in the body. The hands are blue and mottled and slightly œdematous. There is and has been no injury to the skin, such as a burn. Finally, the man acknowledges that he formerly worked in a glass factory and in a brush factory, in both of which factories lead is used. He has no blue line on the gums, and denies lead colic.

In considering such a hypothetical case it should be recalled that hydrofluoric acid is highly corrosive, acting as a powerful caustic on the skin, and that there is practically little if any literature on the

subject. In a case, however, in which it were to do damage by coming in contact with the skin its local corrosive action would be at once manifest. There is no record of its ever having acted by being absorbed and spending its force on the nerves and muscles in the way in which lead does. Finally, in considering this case, it must be recalled that the paralysis is exactly like that caused by lead, and that there is an imperfect history of the man's having worked in factories in which lead occurs.

From all this, is it justifiable to conclude that the man in this hypothetical case is suffering from lead wrist-drop? The jury in this case gave a verdict for the patient.

The hypothetical case was the real case. This is the first instance in which hydrofluoric acid has figured in a medico-legal case, or in which the questions discussed in the above pages, based upon a case of peripheral paralysis, have been brought out in this manner.

PTOMAINS, TOXINS, LEUCOMAINS.

BY

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SINCE the appearance of the article on this subject in the thirteenth volume of this series, published in 1898, several important discoveries have been made. Some of these have led to the settlement of questions which were *sub judice* at that time, while others have demonstrated that opinions held at that time were not altogether correct, and that certain modifications in our views are required. At that time it was still a question whether the specific toxins had their origin in the cleavage action of bacteria, acting as ferments on the complex proteids in the body or in culture media, or were due to synthetical processes by means of which the bacterial cell builds up its own tissue. This question has been practically settled for at least several of the more important microorganisms, and it can be definitely stated that the specific toxins of these are synthetical bodies built up by the bacterial cell, and that the cells themselves contain these poisons. The most decisive work on this subject has been done during the past two years in the writer's laboratory. In 1900 the writer succeeded in perfecting a large incubation tank by means of which bacterial cells may be obtained in large amount free from constituents of the culture medium.* We will give a brief statement of some of the results which have been reached by the study of the bacterial cells obtained by this method.

Bacterial Toxins.

The Colon Toxin.—The study of the composition of the cell of the colon bacillus has been carried on in the writer's laboratory by Cooley, Gelston, Marshall, and Leach. The germ substance after extraction with alcohol and ether forms a grayish-white powder, which takes up and holds moisture, without however absorbing enough materially to

* For a description of this tank see the Transactions of the Association of American Physicians for 1901.

alter its physical condition. This powder when stirred up with water and injected intra-abdominally into guinea-pigs or rabbits is quite highly toxic, causing death in the former animals when used in the proportion of 1: 40,000, and in the latter in still smaller quantities. The toxin cannot be extracted from the cells with alcohol, ether, water, or saline solution; in fact, we have found no solvent which will extract the poison from the cell substance. This toxin is highly resistant to heat, and the powdered germ suspended in water in a sealed tube has been heated for thirty minutes at 184° without appreciable loss in toxicity. The dry germ substance when burned leaves about eight per cent. of ash, a qualitative examination of which shows the presence of sodium, potassium, calcium, aluminum, and copper (the presence of copper is undoubtedly due to the tank in which the germ is grown); also phosphates. The amount of phosphorus contained in the ash was found to be about 2.6 per cent. When the germ substance is shaken with a one-per-cent. solution of sulphuric acid in water and filtered, it is found that the clear filtrate on being treated with three volumes of ninety-six-per-cent. alcohol yields a flocculent precipitate which if not allowed to stand for too long a time under alcohol is readily soluble in water, forming, however, a somewhat opalescent solution. This alcoholic precipitate, when dried first between filter papers and then over sulphuric acid in vacuo forms a white mass, which when rubbed in a mortar is converted into a light gray powder. This powder gives the xanthoproteic reaction for proteids, but responds to the biuret test very imperfectly, and it also fails to give a satisfactory response to the Millon test. It does give the α-naphthol test for furfurol, showing the presence of a carbohydrate. When some of this powdered sulphuric-acid extract of the germ substance is dissolved in water and injected intra-abdominally or subcutaneously into animals it causes death with the symptoms and post-mortem findings practically identical with those observed after administration of the whole germ substance. The part of the germ substance insoluble in dilute sulphuric acid is also poisonous, but much less so than that which is extracted with the acid. It follows from these investigations that the colon bacillus contains an intracellular toxin, which undoubtedly is a substance of complicated constitution, containing two or more toxic groups, one of which is split off by the action of dilute acids. In the case of this bacillus the specific toxin is formed within the cell and does not have its origin in the cleavage action of the bacterium directly or indirectly. The formation of the toxin is a synthetic and not an analytic process. Under ordinary conditions, at least, the toxin contained within the colon bacillus does not diffuse into the culture medium. This is shown by the following experiment: A beef-tea culture which had been grown for twenty-one days in the incubator was

filtered through porcelain. Eight cubic centimetres of the clear sterile filtrate was injected intra-abdominally into a guinea-pig weighing 435 gm. The animal was restless for some time immediately after the injection, probably due to the volume of the fluid used, but gave no other evidence of any effect of the treatment. As a control to this experiment, 0.25 c.c. of the same culture, unfiltered, injected into a guinea-pig of equal weight, killed the animal within twelve hours.

Prolonged heating of the toxin of the colon bacillus with one-per-cent. sulphuric acid destroys its toxicity. This indicates that the toxin undergoes hydrolytic changes under the prolonged heating, which process breaks up its molecule into harmless constituents. Up to the present writing, no attempt has been made to immunize animals to the toxin obtained from the colon bacillus by treating it with dilute sulphuric acid. It remains to be seen whether immunity can be secured to this poison or not, and if immunity be obtained whether or not it extends to the toxin contained in the unaltered germ substance. Marshall and Gelston have carried out a long series of experiments in endeavoring to induce immunity in guinea-pigs and rabbits with the powdered colon germ. With the former animals the result has been practically negative, inasmuch as death has almost invariably resulted before any high degree of immunity has been reached. With rabbits the results have been somewhat more satisfactory, and a few animals have been so far immunized that they have borne one part of the poison to five thousand of body weight. These animals have furnished a serum which has been found to have a preventive influence in rabbits against the toxin, but to be practically without effect in protecting guinea-pigs.

We may sum up the knowledge which has been gained by the above-mentioned studies of the colon bacillus as follows:

(1) The colon toxin is a constituent part of the cell, and is formed by synthetical processes which build up the cell tissue.

(2) This toxin is highly resistant to heat and to chemical agents.

(3) The toxin is undoubtedly of complicated constitution, and contains two or more toxic groups, one of which may be split off by agents which have a hydrolytic action.

(4) The toxin split off from the cell by dilute acids may be deprived of its poisonous properties by the long-continued application of heat, especially in the presence of free mineral acid.

Anthrax Toxin.—Ever since it has been generally admitted that pathogenic bacteria produce their harmful effects by the elaboration of poisons, investigators have endeavored to find the specific toxin of anthrax. At one time Hoffa claimed that he had found a basic substance, to which he gave the name anthracin, and which he believed

to be the specific poison of this disease. Subsequent investigations, however, have shown that this substance cannot be considered the specific poison of anthrax, and moreover no one else has ever succeeded in obtaining it at all. The work of Martin and that of Marmier, referred to in my article upon this subject in Vol. XIII. of this series, have also been shown to be without merit. Without going fully into the literature of this subject, which is quite voluminous, the writer may refer to a research by Conradi, in which the work of previous investigators is reviewed, and is followed by a statement of his own researches. Conradi attempted to solve the question of the existence of an anthrax toxin by the following methods: (1) Exudates obtained from the peritoneal cavities of guinea-pigs inoculated with anthrax were filtered through porcelain filters and injected into rabbits in quantities of from 10 to 20 c.c. without effect. (2) The organs of guinea-pigs which had succumbed to anthrax were rubbed up with sterilized sand, diluted with physiological salt solution, filtered through porcelain, and injected into rats, guinea-pigs, and rabbits without effect. (3) Collodion sacs were filled with cultures of anthrax and placed in the abdominal cavities of susceptible animals, where they remained without detriment to the health of the animal, thus showing that the anthrax bacillus does not produce any soluble toxin. In fact, this had been demonstrated as early as 1877 by Pasteur, who filtered both the blood of animals sick with anthrax and artificial cultures through porcelain and injected the germ-free filtrate into animals, without inducing any disease. (4) The peritoneal exudates obtained from animals dead with anthrax were sterilized by prolonged and frequent shaking with toluol, and injected into susceptible animals, without effect. (5) Asporogenous cultures were deprived of vitality by exposure for one hundred and ten hours to $-16°$, and after having been shown to be sterile by being kept for some time in the incubator, were injected into susceptible animals without effect. (6) Anthrax cultures were exposed to hydraulic pressure of five hundred atmospheres, and the fluid thus obtained, after filtration through porcelain, was injected into animals without effect. (7) The experiments of Brieger and Fraenkel, who at one time reported the preparation of an anthrax toxalbumin, were repeated with negative results.

From these experiments Conradi reached the following conclusion: "By no method known at present can it be shown that the anthrax bacillus forms either an extracellular or an intracellular poison in the animal body; indeed, these experiments increase the probability that the anthrax bacillus does not form any poisonous substance. Therefore the solution of the manner in which anthrax infection results remains unknown. Whether improved chemical methods will lead to the detection of a poison or not cannot be predicted, but for the pres-

ent the anthrax bacillus must be regarded as a purely infectious microorganism."

Recently experiments have been carried out in the writer's laboratory by J. Walter Vaughan, which apparently offer a satisfactory solution of the question of the existence of anthrax toxin. A large amount of germ substance was obtained by the method already referred to in discussing the colon toxin, and the bacterial powder was heated with one-per-cent. sulphuric acid in the autoclave at 110° for ten minutes. The clear filtrate obtained with the dilute acid on being treated with three volumes of ninety-per-cent. alcohol deposited a white flocculent precipitate, which when collected, dried, and pulverized, was found to be soluble in water and killed guinea-pigs with all the symptoms and lesions of anthrax when injected into the abdominal cavity in doses of from 50 to 100 mgm. It was also found that the part of the germ substance undissolved by the dilute acid is poisonous, but much less so than that part split off by the acid. The following conclusions have been reached from this study of the anthrax toxin:

(1) The anthrax bacillus does produce an intracellular toxin, which contains two or more toxic groups, one of which is split off by means of dilute sulphuric acid at the temperature of 110°.

(2) The split toxin is deprived of its poisonous properties by continued heating in the presence of free mineral acid.

(3) The toxin split off by dilute acid is probably basic in character, and possibly belongs to a low order of proteid substances, since it does not respond to the biuret or Millon test, but does give the xanthoproteic reaction.

It seems evident from this work on the chemistry of the anthrax cell that the bacillus in the animal body must undergo certain hydrolytic changes by means of which its toxic constituent is set free. Whether this process of setting the toxin free is a passive one and due to the normal disintegration of the dead cell, or is accomplished by the activity of certain cells in the animal body, remains for future investigations to determine. It seems altogether likely that the cells of the animal body in resisting the invasion of the bacterial cells split them up, and in so doing liberate the poison which destroys the life of the animal. However, this is a matter of speculation, and any authoritative statement on this subject must await more elaborate investigation.

The Diphtheria Toxin.—Ehrlich's remarkable theory concerning the action of toxins and antitoxins and the mode of formation of the latter is based upon a large number of carefully conducted experiments with the toxin and antitoxin of diphtheria. The essential points in Ehrlich's theory are as follows:

(1) Toxins and antitoxins neutralize one another after the manner

of chemical reagents. The chief reasons for this statement lie in the observed facts, (*a*) that neutralization takes place more rapidly in concentrated than in dilute solutions, and (*b*) that warmth hastens and cold retards neutralization. From this Ehrlich concludes that toxins and antitoxins act as chemical reagents do in the formation of double salts. A molecule of the poison requires an exact and constant quantity of the antitoxin in order to produce a neutral or harmless substance. This implies that the specific atomic group in the toxin molecule combines with a certain atomic group in the antitoxin molecule.

(2) The antitoxin is a reaction product of the living organism, and not a transformation product of the toxin introduced in securing immunity. According to Ehrlich, when the toxin is introduced into the animal body in small quantities it combines with certain side chains in the molecules of the living cells. These side chains are supposed to be necessary for the proper functioning of the cells, which, finding themselves deprived in part of their function on account of combination with the toxin, produce other side chains and some of these are cast off into the blood and constitute the antitoxin. As an illustration: When a small quantity of tetanus toxin is introduced into the animal body it combines with certain side chains of the molecules of the cells of the central nervous system, and renders these atomic groups useless so far as the nutrition of the cell is concerned. In order to compensate for its loss, the cell produces another side chain similar to the one of which it has been deprived. Being called upon repeatedly to exercise this activity, there is not only compensation, but overcompensation, and the result is that more side chains are formed than the cell can use, and these break off and float away in the blood, constituting the antitoxin. Moreover, the atomic group or side chain, after being liberated from the cell, may possibly acquire greater avidity for combination with the toxin; or, in other words, the toxin will combine more readily with these side chains when free and floating in the blood than when they constitute parts of the molecules of cells.

(3) Diphtheria toxin as it exists in sterilized cultures is composed of equal parts of toxin and toxon. The latter has no serious effect upon animals. It may cause local œdema, but it never kills. The toxon, which may be regarded as inert, has quantitatively the same power of combination with antitoxin as is possessed by the toxin, but combines with the antitoxin with less avidity.

(4) The well-known fact that crude diphtheria toxin decreases in toxicity on standing is explained by supposing that there is a gradual conversion of the toxin into toxon, while the other equally well observed fact that the toxin of diminished toxicity requires the same amount of antitoxin for its neutralization as the original toxin did,

is explained by the theory that toxon and toxin combine with antitoxin in the same proportion.

Gelston has shown that in addition to the soluble diphtheria toxin which exists in cultures of this bacillus there is also an intracellular toxin. Moreover, he finds that commercial diphtheria antitoxin, while it protects animals against the soluble poison, fails to afford protection against the cellular toxin. This undoubtedly explains the fact which has been observed by others that certain animals practically immune to diphtheria toxin are not immune to diphtheria infection. Whether or not an antitoxin for the cellular toxin of diphtheria can be produced in animals artificially remains to be determined. The relation between the cellular toxin and the soluble poison also opens up a question of interest and importance, which must be solved by future investigations.

The Tetanus Toxin.—The researches of Ehrlich have demonstrated that the tetanus bacillus produces two toxins, tetanospasmin and tetanolysin. To the first of these the tetanic convulsions are due, while the second has a hæmolytic action. These toxins do not always exist in the same proportion in a given culture and for this reason one culture may have a marked tetanic effect, and manifest but little hæmolytic action, while a second culture may readily dissolve blood corpuscles and show but slight action on the nervous system. These toxins differ in their stability, the hæmolytic poison being less stable and undergoing complete destruction when heated to 50° for twenty minutes. When blood corpuscles are added to a tetanus culture the greater part of the tetanolysin, possibly the whole of it, combines with the corpuscles, while the tetanospasmin remains in solution. On the other hand, if an emulsion of nerve cells be added to a tetanus culture the tetanospasmin combines with these cells, while the tetanolysin remains in solution. Each of these toxins has its specific antitoxin, and in the blood of animals immunized with tetanus cultures one or the other antitoxin may predominate; and in this way it happens that a given serum may be strongly antispastic, while it is but slightly antilytic, or the reverse may be true.

Madsen has made a special study of tetanolysin obtained by precipitation of a bouillon culture of the tetanus bacillus with ammonium sulphate. This poison dissolves the red corpuscles of the horse, sheep, goat, and rabbit; the blood of the horse and that of the rabbit being found to be especially susceptible while that of the goat is less so. For experimental purposes the defibrinated blood of the rabbit, diluted with eighty-five per cent. of common-salt solution to five per cent. is suitable, and this diluted blood may be placed in tall test tubes for purposes of demonstration. To tubes thus prepared varying quantities of the poison may be added, and the mixture allowed to stand for

one hour at 37° and then kept over night at a low temperature. In this way the effects of different quantities of the poison are made plainly manifest to the eye. In those tubes containing the larger quantities of the tetanolysin, all the corpuscles are dissolved, and there remains only a blood-red solution, uniform in tint from top to bottom. As the amount of the poison is diminished in the tubes the number of undissolved corpuscles collected at the bottom is increased and the color of the supernatant fluid grows less intense toward the top. Madsen found that when larger quantities of the poison are used the destruction of the blood corpuscles is practically instantaneous and occurs before there is time for subsidence, while in more dilute solutions the corpuscles partially subside before they are acted upon by the toxin. This shows that there is a latent period in the action of the poison and that this period increases as the quantity of toxin is diminished. Furthermore, it was found that lowering the temperature increases the latent period, and it is highly probable that individual corpuscles vary markedly in their resistance to the hæmolytic action of this toxin.

Continuing his work, Madsen has shown that the hæmolytic action of the tetanolysin can be neutralized by the action of an antitoxic serum. His conclusions from his studies of tetanolysin are stated as follows:

(1) In cultures of the tetanus bacillus there is besides tetanospasmin another poison, tetanolysin, for which there may be produced a specific antitoxin, which may be designated as antilysin.

(2) The action of this lysin and its anti-body can be measured with exactness in the test tube, by methods of color comparison.

(3) Tetanolysin combines with the red blood corpuscles, and the combination is preceded by a latent period which is variable, and is dependent upon the temperature and the amount of the poison.

(4) Experiments show that tetanolysin presents a complicated neutralization reaction which indicates a close resemblance to the diphtheria toxin.

(5) Tetanolysin probably consists of two substances, and one of these of three sub-bodies, which may be known as prototoxin, deuterotoxin, and tritotoxin.

(6) The prototoxin makes up only one-third of the poison, but possesses one-half of the hæmolytic action.

(7) The deuterotoxin makes up one-ninth of the poison, but possesses two-fifths of the total hæmolytic action.

(8) The tritotoxin makes up one-fourth of the poison, but possesses only one-tenth of the poisonous action.

(9) The second half of the toxin possesses only minute toxicity, and may be known as toxon.

(10) In tetanolysin, as in diphtheria toxin, there are two groups, a haptophorous group, by which the substance combines with antitoxin, and the toxophorous group, by which the combination with the red blood corpuscles and the hæmolytic action are effected. Of these groups, the first one is relatively stable, while the latter is easily converted into a toxoid.

(11) It is probable that tetanospasmin has a neutralization structure similar to that possessed by tetanolysin.

It has been shown by Ransom that both the toxin and antitoxin of tetanus pass without change from the blood into the lymph. Shortly after the intravenous injection of the toxin it is found equally distributed in the blood and lymph, while the antitoxin remains in excess in the blood. These observations indicate that the toxin behaves like an inorganic substance in passing from the blood into the lymph, while in this respect the antitoxin resembles the proteids of the blood.

Wassermann and Takaki have shown that the tetanus toxin combines with nervous tissue, forming an inert substance. They prepared a solution of tetanotoxin, which was preserved by the addition of an equal volume of glycerin. The strength of this solution was such that 0.001 c.c. sufficed to kill mice in the course of three days. A quantity equal to from one to ten fatal doses of this solution was rubbed up into an emulsion with the substance of the spinal cord or brain, and this mixture injected subcutaneously into mice. For control, equal quantities of liver tissue were mixed in the same way with tetanotoxin, and likewise injected into mice; while as a further control, corresponding amounts of the tetanus poison without mixture with any tissue were injected. By these experiments it was shown that the normal cord and brain form an inert compound with the toxin of tetanus, while none of the other organs has any such effect. The antitoxic action of the cord was found to be less marked than that of the brain substance. This is somewhat surprising, inasmuch as the symptoms manifested in tetanus are generally believed to be referable to the action of the toxin on the cord rather than on the brain. These experiments apparently demonstrate that chemical combination takes place between the toxins introduced into the body and the nerve cells.

It has been shown by Roux and Borrell that small doses of tetanus toxin when injected directly into the brain substance kill animals, while much larger quantities of the same poison are required when the injection is made subcutaneously or intraperitoneally. This is explained by supposing that when intracerebral injection is made all of the toxin combines with the side chains of the brain cells, inflicting upon this tissue an injury to which the animal succumbs.

The Toxins of Suppuration.—It has been ascertained by Van de Velde that the staphylococcus pyogenes produces a substance which

destroys leucocytes and for which the name leucocidin has been proposed. This investigator injected sterilized cultures of the staphylococcus into the pleural cavities of rabbits and studied the exudate which formed. He soon ascertained that the leucocytes present in such an exudate in large numbers undergo characteristic changes. He next added to small quantities of the exudate living healthy leucocytes and observed that these underwent like transformations. Heating the exudate for ten minutes at 58° destroys its action on leucocytes. The successive steps in the destruction of the white blood corpuscles are described as follows: (1) The leucocytes draw in their pseudopodia and become round. (2) A light zone appears in the periphery, while the centre remains granular. (3) The light zone gradually extends, and granulation completely disappears. (4) The corpuscles are reduced to empty sacs, with scarcely discernible nuclei, which at last wholly disappear. These degenerative changes are completed in about two minutes, and similar alterations are observed in leucocytes added to either non-virulent or virulent cultures of the staphylococcus. Confirmatory observations have been made by Bail and Lingelsheim, and Denys and Van de Velde have found that the serum of animals which have been rendered immune to the staphylococcus pyogenes aureus destroys the leucocidin present in cultures of this organism. A method of measuring the effects of leucocidin has been devised by Neisser and Wechsberg, who have come to the conclusion from their investigations that typical pyogenetic staphylococci, both the aureus and albus, produce the same leucocidin, but that there are varieties of both these organisms which do not elaborate this toxin.

It was first observed by Kraus that red blood corpuscles are destroyed when placed in filtered cultures of the staphylococcus, and the hæmolysin of this germ has been further investigated by Neisser and Wechsberg, who have designated it staphylolysin. It is probable that this toxin is possessed of a constitution similar to that attributed to the diphtheria toxin, according to Ehrlich's theory, and that it consists of a toxin and a toxon. Furthermore, it seems probable that the toxin may be converted into toxoids, but while the toxoids of the diphtheria toxin have the same avidity for antitoxin as that possessed by the toxin, the toxoids of staphylolysin combine with antitoxin with less avidity than do the toxins. The blood serum of healthy men contains an antistaphylolysin, but the strength of this varies greatly in different individuals. After the intravenous injection of both sterilized and unsterilized cultures of the staphylococcus in rabbits Ribbert observed changes in the kidneys, heart, and lungs, spleen and bone marrow which he attributes to the action of the toxin because they are found after the injection of sterilized as well as after the employment of living cultures. These changes are characterized by the presence

of infarcts and abscesses. Neisser and Wechsberg describe the pathological conditions found in the kidneys of animals which they have rendered immune to the staphylotoxin by intravenous injections as follows: In the cortex one recognizes three zones, which, proceeding toward the centre, are as follows: (1) A circular irregular zone, in which the tubuli contorti are for the most part destroyed, and the peritubular spaces are filled with the fragments of broken-down leucocytes. (2) An intermediate zone in which the leucocytic reaction is less marked, but in which necrosis of the epithelium is plainly seen. Relatively few of the epithelia of the tubuli contorti possess nuclei, and even these show evidence of cell disintegration. Most of the cells are without nuclei and appear in a state of coagulation necrosis. Hyaline casts and fragments of broken-down leucocytes are found in the uriniferous tubules. In this zone the glomeruli are altered and one may observe all changes from simple hyperæmia to complete necrosis in which there is no sign of a glomerulus left except a structureless capsule. (3) The third zone is also rich in broken-down leucocytes, especially in the peritubular spaces. Some of the blood-vessels are still patent while others are filled with thrombi consisting of fibrin and disintegrated leucocytes. These authors were unable to demonstrate that the changes in the kidney are due directly to the staphylotoxin, and they have provisionally named the poison which induces these lesions "nephrotoxin."

The Gonococcus Toxin.—The effects of sterilized cultures of the gonococcus have been studied by Christmas, Nikolaysen, and Wassermann. These studies have demonstrated that cultures in which this microorganism has been destroyed by heat are as virulent to the lower animals as are living cultures. It has also been shown that the gonotoxin is contained within the cell of the microorganism, for if a culture two days old is filtered through porcelain and the filtrate is injected into mice, but little or no effect results, while if a culture from one to three weeks old is treated in like manner the filtrate is found to be toxic. This indicates that the toxin is originally contained within the cell, and becomes active only after the disintegration of the organism. Different cultures have been found to vary markedly in their toxicity. It was found by Wassermann that while 0.1 c.c. of certain sterilized cultures sufficed to kill mice, 1 c.c. of other cultures was necessary in order to accomplish a like result. Gonotoxin is a relatively stable body and can be precipitated from sterilized cultures with absolute alcohol, and can be heated to 100° without marked loss of toxicity. While man is the only beast susceptible to gonorrhœal infection, many of the lower animals, such as rabbits, mice, and guinea-pigs are readily affected by the toxin. That this toxin has a pyogenic action can easily be shown by injection of a small quantity into the

anterior chamber of the eye of a rabbit. Corneal cloudiness, hypopyon, and sometimes complete loss of the eye result. Wassermann injected 0.1 c.c. subcutaneously into his own arm, and found that after about four hours the place of injection became painful and subsequently he had light chills followed by a temperature which reached 38°. There were also headache and pain in the joints, but all symptoms disappeared after two days. The same experimenter has tried this agent in the treatment of obstinate cases of chronic gonorrhœa, but has found that the toxin not only is without curative effect, but intensifies the symptoms. Both Wassermann and Christmas have attempted to produce an antitoxin for this poison, but without any marked success. It is true that the latter has reported the preparation of an active serum by immunizing goats, but the action of the antitoxin thus obtained was very slight, while Wassermann's results were wholly negative. When small quantities of gonotoxin are introduced into a sound urethra, suppuration appears after a few days. The action of gonotoxin as observed in these laboratory experiments explains the clinical course of many cases of gonorrhœa. When the infection is confined to the anterior urethra, the germ may soon die and the toxin be washed out with the urine, but when the infection is in the posterior urethra some of the microorganisms find their way into the crypts of this region, and may pass through many generations, elaborating their toxin, and causing a continued formation of pus. These observations also explain why this disease is likely to be so much more serious in woman than in man.

The Toxin of the Tubercle Bacillus.—According to Ruppel, there are three kinds of fatty or waxy substances in the tubercle bacillus. The first constitutes about eight per cent. of the total weight of the dried germ substance, from which it can be removed with cold alcohol. In the process of extraction the alcohol becomes markedly red, and this is believed to be due to a chromogen contained in the bacillus and which develops into the coloring matter on exposure to air. When this alcoholic extract is evaporated there remains a smeary mass consisting largely of free fatty acid. This substance is easily saponified, and contains together with the free fatty acids a substance soluble in ether, which is believed to be one of the higher alcohols. The second fatty body contained in the bacillus may be extracted from the residue left after the action of cold alcohol by means of hot alcohol. This substance saponifies with difficulty, and appears to consist of fatty esters of the higher alcohols. The third fatty body may be removed from the residue left from previous extractions with ether. On being heated it gives off an odor similar to that of beeswax. The total amount of fatty substances contained in the tubercle bacillus varies from eight to twenty-six per cent.

According to Ruppel, when tubercle bacilli have been finely pulverized they give up about half their substance to aqueous extracts, and when the finely divided powder is shaken with water there is formed a milky emulsion, which when placed in the centrifuge separates into a transparent feebly opalescent yellowish fluid, and a deposit. The deposit when dried and weighed is found to constitute about one-half the weight of the powdered bacilli originally taken. The reaction of the aqueous extract is generally feebly alkaline, although it may be neutral. It contains no coagulable proteid, and of the general color reactions it responds only to the biuret test. When acidified with acetic acid a precipitate insoluble in excess, but freely soluble in dilute alkalies is formed. This precipitate contains something more than four per cent. of phosphorus. It responds to neither the Millon nor the xanthoproteic test, but does give the biuret reaction. When dissolved in glacial acetic acid and warmed with sulphuric acid it does not give a red coloration. Ruppel treated 25 gm. of this substance with one-per-cent. sulphuric acid and precipitated the acid extract thus obtained by the addition of absolute alcohol. This precipitate consists of a snow-white flocculent powder, and the amount obtained in this experiment was 0.7 gm. When dissolved in warm water and precipitated with barium hydrate and filtered it was freed from the sulphuric acid with which it was combined and from this filtrate the proteid body was precipitated with alcohol. Ruppel believes it to be a protamin, and proposes for it the name "tuberculosamin." He thinks that in the tubercle bacillus this protamin is combined with nucleinic acid and from the part insoluble in one-per-cent. sulphuric acid he obtained a nucleinic acid containing 9.42 per cent. of phosphorus. He proposes that the nucleinic acid in the tubercle bacillus be designated as tuberculinic acid.

Behring states that the tuberculinic acid as prepared by Ruppel contains a histon-like body, on the removal of which the tuberculinic acid may be obtained chemically pure. To this substance he attributes the toxic action of tubercle bacilli, and he states that 1 gm. of tuberculinic acid is capable of destroying the life of 600 gm. of normal guinea-pig when injected subcutaneously, and 90,000 gm. when introduced intracerebrally; and that the same amount of tuberculinic acid is capable of destroying the life of 60,000 gm. of guinea-pig already infected with tuberculosis, when injected subcutaneously, and 40,000,000 gm. of the same tissue when injected intracerebrally. In distinguishing by physiological experimentation between tuberculinic acid and other nucleinic acids, tuberculous animals should be selected on account of their greater susceptibility to the former.

Levene has obtained from samples of tubercle bacilli grown on different culture media different nucleinic acids, which vary in phos-

phorus content from 6.58 to 13.9 per cent. He has also obtained a glycogen-like body from the tubercle bacillus. This substance gives an opalescent solution, which on the addition of iodine colors similarly to glycogen, and on being heated with mineral acids reduces Fehling's solution.

The Specific Precipitins.

Kraus found that when cultures of the cholera bacillus were freed from germs by filtration through porcelain, and after having been proved to be sterile were treated with different quantities of the sterile serum of an animal which had been immunized to cholera, a precipitate formed. More extended investigation demonstrated that the germ-free bacterial culture and the serum must be homologous in order to obtain this precipitation. A serum obtained from an animal which has been immunized to the cholera bacillus when added to filtered cultures of this microorganism gives a precipitate, but gives no cloudiness when added to like cultures of any other germ. Furthermore, it was found that the serum of non-immunized animals does not give precipitates with the filtered cultures of any of the pathogenic bacteria. Kraus extended his investigations and employed the sera and filtered cultures not only of cholera, but also of typhoid fever and the plague, and found that the reaction observed by him was a specific one, inasmuch as it was obtained only with homologous sera and bacterial filtrates, and not with heterologous fluids.

The investigations of Kraus were soon repeated and confirmed by Nicolle, and subsequent investigations by others have shown that this specific reaction holds good with all bacteria to which animals have been immunized. The substance in the serum which enters into this reaction is known as the precipitin, and the precipitate formed is designated as the precipitum. Bordet found that when milk partially sterilized by being heated for one hour at 65° is injected intraperitoneally, and this injection is repeated at short intervals for some time, the blood serum of the animals thus treated gives with the milk which has been injected a precipitate. Wassermann and Schütze demonstrated that the serum of a rabbit treated with cow's milk gives a precipitate with cow's milk, and not with the milk of any other animal, and that rabbits treated with goat's milk furnish a serum that gives precipitates with goat's milk and with no other milk; and the same holds good when the experiments are made with woman's milk. The following are the details of an experiment of this kind: Several rabbits were treated subcutaneously or intraperitoneally at intervals of from three to four days with from 10 to 50 c.c. of cow's milk, sterilized with chloroform, while a like number were treated in the same way with goat's milk, and a third lot treated with woman's milk. After the

rabbits had undergone this treatment for about three weeks and each had received about 100 c.c. of milk, they were bled and their sera, diluted 1: 5, were added to milk diluted 1: 40 and these mixtures allowed to stand at room temperature for some hours. It was found that the serum from the rabbits treated with cow's milk precipitated the albuminous substances in cow's milk, but had no such action on the milk of either woman or goat; while the serum of the rabbits treated with goat's milk precipitated the casein of goat's milk and had no effect upon that of the woman or cow, etc. The serum of the animals immunized with milk is designated lactoserum, and it has been found that the lactosera have in all cases a specific reaction. These investigations demonstrate most conclusively that the proteids of milk of each species of animal differ from those of every other species, and they certainly should convince us that it is impossible by any chemical process to make cow's milk a perfect substitute for mother's milk in the feeding of infants. Fisch injected animals intraperitoneally with emulsions of the cells of the udders of animals, and found that he could obtain in this way specific lactosera. This indicates that milk is not a mere filtration product, but that some of its important constituents result from the transformation of the specific cells of the gland.

Myers treated rabbits intraperitoneally with crystals of egg albumen and obtained sera which gave dense precipitates when added to solutions of crystallized egg albumen. These precipitates were found to form at ordinary temperature, but more quickly and abundantly at 37°. The precipitum is soluble in two-per-cent. sodium-chloride solution, and such a solution gives the ordinary proteid reactions. The serum of a rabbit treated with egg albumen from the fowl forms a slight precipitate with the albumen obtained from duck's eggs. Ovasera have no precipitating action on globulin obtained from sheep serum, nor on that from bullock serum, nor on serum albumin from the sheep or the bullock, nor on peptone. Uhlenhuth broke fresh eggs in sterilized beakers, diluted with physiological salt solution, stirred with sterilized rods, and in this way prepared a solution which could be easily injected intraperitoneally into rabbits. He introduced into each animal at each time the whites of from two to three eggs, and notwithstanding the large volume of the fluid, which frequently measured 100 c.c., it was well borne. After this operation had been repeated several times he obtained ovasera which proved to be most delicate reagents in testing for egg albumen, inasmuch as a few drops of such a serum added to egg albumen diluted with 100,000 parts of water gave a distinct cloudiness, while nitric acid and acetic acid and ferrocyanide of potassium failed to indicate the presence of albumin when the solution was diluted only 1: 1,000. This reaction is specific

and these ovasera do not give precipitates with alkaline albuminates, peptones, casein, or blood serum. However, it was found that ovasera obtained from animals immunized with hen's eggs reacted with the albumen of pigeon's eggs. Ovasera may be heated for one hour at 60° without injury to their precipitins.

Leclainche and Vallee have obtained urinsera by treating animals intravenously with albuminous urine. A serum of animals thus treated furnishes a delicate test for albuminous urine, giving an immediate precipitate. Moreover, if the animal has been rendered immune with a urine containing serum globulin, a serum from this animal does not precipitate urine containing serum albumin, and *vice versa*. Urinsera also precipitate pleuritic and other exudates, thus showing that the proteids of albuminous urine and of these exudates are in part at least identical. There has been some contradiction in the statements concerning the action of urinsera on the blood serum of man, and this point needs further investigation. Zuelzer injected from 5 to 10 c.c. of albuminous urine containing from 1 to 9 per mille of albumin at intervals of from one to three days for two weeks, and obtained from the animals thus treated a serum which precipitated both albuminous urine and the blood of man.

Bordet treated rabbits with the defibrinated blood of the chicken and obtained from the former a serum which produced a precipitum in chicken's blood. Wollf permitted chicken's blood to flow into four times its volume of a one-per-cent. solution of salt, and separated the corpuscles and the plasma and injected these separately into two sets of rabbits. From four to six injections at intervals of four or five days were made, and only those animals treated with the blood plasma yielded a precipitum with chicken's blood. Other rabbits treated in like manner with dog's blood corpuscles and plasma gave similar results; the precipitins being found only in those animals which had been treated with the fluid portion of the blood. Uhlenhuth treated rabbits intraperitoneally at intervals of from six to eight days with defibrinated blood, and after the fifth injection he obtained a serum which was used in testing blood from various sources. The blood to be tested was diluted with tap water, 1 : 100, and was freed from stroma either by filtration or by decantation. Then 2 c.c. of this diluted blood was placed in each of a series of test tubes and diluted with an equal volume of double physiological salt solution. Blood thus prepared was obtained from the ox, horse, donkey, pig, sheep, dog, cat, deer, hare, guinea-pig, rat, mouse, rabbit, chicken, goose, turkey, pigeon, and man. To tubes containing these samples of diluted blood from six to eight drops of the serum of the rabbit which had been treated with ox blood was added. The ox blood was immediately clouded, while all others remained perfectly clear. The clouding in

the first mentioned grew in intensity and finally formed floccules which eventually subsided. Thus it was shown that by this test ox blood could be distinguished from all others with which it was compared. Like tests were made with blood stains from man, the horse, and the ox, four weeks after the stain had been deposited. Stern immunized animals to human blood, and tested the serum thus obtained upon blood from diverse sources. He found that the reaction is not wholly a specific one, inasmuch as the serum obtained in his experiments gave marked cloudiness with sera prepared from three different species of ape. Wassermann and Schütze have also found that the blood of the baboon gives a precipitum when treated with the serum of an animal immunized to human blood. Nuttall immunized rabbits with the blood of man, dog, sheep, ox, and horse, and the sera thus obtained were tested against thirty-six kinds of blood. He found that the serum of rabbits treated with human blood produced a marked precipitum only in human blood solutions, but the blood of four species of monkeys gave a slight but distinct reaction, and a very faint clouding appeared in solutions of the blood of the horse, ox, and sheep, while all other bloods remained perfectly clear.

The Lysins.

Pfeiffer found that if cholera bacteria are placed in the peritoneal cavity of a guinea-pig which has been immunized to cholera, the bacterial cells are dissolved by the peritoneal fluid. If such an injection be made and portions of the bacilli be removed every five minutes, it can be plainly seen under the microscope that the bacterial cells are undergoing solution in the surrounding fluid. The bacilli lose their motility, swell up, and break into granules which gradually melt away into the fluid. Extended investigations have shown that this reaction is specific, and the same phenomenon may be observed in animals which have been immunized to the typhoid bacillus or other pathogenic microorganisms. Moreover, when a mixed bacterial culture is subjected to this test the peritoneal fluid dissolves the bacteria of the species against which the animal has been immunized and leaves all other bacteria untouched. Metchnikoff found that Pfeiffer's phenomenon, which is also known as bacteriolysis, may take place in vitro when to a mixture of cholera serum and the cholera culture there be added a small quantity of the peritoneal exudate from a normal guinea-pig, and Bordet added the observation that cholera serum in and of itself suffices to induce bacteriolysis in vitro when it is perfectly fresh. On long standing it becomes inactive, but its activity even then may be restored by the addition of a small quantity of normal serum. Bordet injected guinea-pigs at intervals with the

defibrinated blood of rabbits and obtained from the former a serum which *in vitro* dissolved the blood corpuscles of the latter with great intensity, while the serum of normal guinea-pigs was found to be without solvent action upon the corpuscles of the rabbit. The hæmolytic properties of the serum obtained in these experiments were found to be destroyed at 55°, but it was soon ascertained that the serum rendered inactive by the above-mentioned temperature could be regenerated on the addition of certain amounts of the serum of either normal guinea-pigs or rabbits. Ehrlich and Morgenroth treated a goat at irregular intervals for eight months with subcutaneous injections of defibrinated sheep's blood, diluted with 0.85-per-cent. salt solution until the mixture contained only five per cent. of blood. The serum of this goat rapidly dissolved the erythrocytes of the sheep *in vitro*, while the serum of a normal goat had but slight solvent action on the blood corpuscles of the sheep. When the immune serum was heated for half an hour at 56° it lost its solvent action, but on the addition of the serum of a normal animal its activity was regained. The added serum was active when obtained from either the goat or the sheep, but less so from the latter. It was demonstrated by Ehrlich and Morgenroth that the hæmolytic action of blood serum is dependent upon the presence of two substances, one of which is thermostable, and remains unaltered when heated to 56°, while the other is thermolabile, or is destroyed at the above-mentioned temperature. The thermostable substance is now known as the intermediary body, sometimes called immune body, while the thermolabile substance, formerly known as addiment, is now designated as complement. The intermediary body has two haptophorous groups, one of which is possessed of great avidity, and it is by means of this that the intermediary body combines with the corpuscles, and its great avidity is shown by the fact that this combination takes place even at 0°. The other haptophorous group of the intermediary body is possessed of less avidity, and it is by means of this that combination between the intermediary body and the complement takes place, and on account of the slight avidity of this haptophorous group, this combination occurs only at a relatively high temperature. When an active serum is kept at 0° it contains the intermediary body and the complement both in the free state. Now, if susceptible erythrocytes be added to this serum, still kept at 0°, the corpuscles and the intermediary body combine, while the complement remains free, but when the temperature is raised to 37° the complement enters into the combination by attaching itself to the intermediary body. The haptophorous group, by which the intermediary body combines with the corpuscle, is sometimes designated as hæmotropic. There may be in certain sera intermediary bodies whose hæmotropic groups have no greater avidity than their complements, or there may

be complements which combine with intermediary bodies at a low temperature. It may happen that the intermediary body is contained in the serum of one animal while the complement is furnished by the blood of another. This has been shown to be the case in the following experiment: Dog's serum dissolves the erythrocytes of the guinea-pig with great energy. If the dog's serum be heated to 57° it loses its hæmolytic action on guinea-pig blood, but if inactive dog serum be added to 5 c.c. of a five-per-cent. dilution of guinea-pig blood, and 2 c.c. of the serum of a normal guinea-pig be added to this mixture, complete hæmolysis occurs. This is explainable only on the supposition that the intermediary body exists in the dog's serum, while the complement is furnished by the serum of the guinea-pig. In this case the complement is furnished by the serum of the animal whose corpuscles are dissolved. Ehrlich suggests that the hæmolytic action of the blood serum of one animal upon the corpuscles of another species be designated as heterolysis, and the active agent or agents in the hæmolytic serum in this case be termed heterolysins, while the hæmolytic action of the serum of one species on the corpuscles of another individual of the same species be designated as isolysis, and the active agent as isolysin. If a serum should be found which dissolves the corpuscles of the individual from which the serum has been obtained, the process would be designated autolysis, and the active agent as autolysin. No one has yet discovered an autolysin, although the possibility of the existence of such a substance cannot be denied. It is probable that certain diseased conditions which we have hitherto designated as autointoxication may be caused in this way. Ehrlich designates the haptophorous group in the corpuscle, or the side chain in the corpuscle which combines with the intermediary body as the "receptor." He supposed that it is by the action of these receptors that hæmolysins, and other toxins as well, combine with and destroy the cells of the body. If there be no receptors the intermediary body cannot combine with the corpuscle, and consequently there is no hæmolysis. Antihæmolysins are supposed to be formed in the body of the animal treated with hæmolytic serum in the same way that antitoxins are formed in the bodies of animals immunized to the toxins. If a hæmolytic serum be injected into an animal in small but gradually increased doses at intervals, immunity to such serum is obtained, and the serum of the animal thus immunized contains an antihæmolysin. When a small amount of the hæmolytic serum is injected it is taken up by the receptor in the blood cell, and provided that the amount of the hæmolytic serum injected is small, the blood corpuscle is not destroyed; and needing for the performance of its function the receptor which has combined with the hæmolysin, it throws out other receptors, and, as in the case of the production of antitoxin, a point

is reached when there is over-production of receptors, and those not needed by the cell and not taken up by the hæmolysin are cast off into the blood and constitute the antihæmolysin. Ehrlich likens the intermediary body to diazo-benzaldehyde, which by means of its diazo group is capable of combining with aromatic amides, phenols, etc., while by means of its aldehyde group it may combine with the hydrazins, mono-radicles, and hydrocyanic acid. Phenol and hydrocyanic acid do not directly combine, but with diazo-benzaldehyde acting as an intermediary body these two substances can be brought into combination. In this illustration we may say that the aromatic body or the phenol represents a constituent of the blood corpuscle,—the diazo-benzaldehyde is the intermediary body, while the poisonous hydrocyanic acid constitutes the complement. As has already been stated, the intermediary body is possessed of two haptophorous groups. By means of one of these it effects combination with the receptor of the cell, while by means of the other it combines with the complement. The former may be designated as the cytophil group, while the other may be characterized by the designation of complementophil. There may be two or more kinds of intermediary body in a given blood serum. Ehrlich has demonstrated this in the following observation: The serum of a rabbit immunized to ox blood has a hæmolytic action not only upon the corpuscles of the ox but also upon those of the goat. If such a serum be treated with a sufficient amount of the corpuscles of the ox, and the mixture separated in a centrifuge, the supernatant fluid has no solvent action upon either ox or goat corpuscles. This indicates that the ox corpuscles have taken up all the intermediary bodies in the blood serum. However, if this serum be mixed with goat corpuscles and the mixture be separated in the centrifuge, the supernatant fluid has no solvent action upon goat corpuscles, but still possesses solvent action upon ox corpuscles. This demonstrates that there are in the serum of the rabbit immunized to ox blood at least two intermediary bodies, both of which are capable of combining with ox corpuscles, while only one combines with goat corpuscles. Intermediary bodies differ both in their cytophil and in their complementophil groups. A given intermediary body unites with a corpuscle only when it finds in that corpuscle its appropriate receptor or receptors; and the receptors in one and the same corpuscles may differ and take up different intermediary bodies. In the same way every intermediary body will not combine with every complement, and combination between the intermediary body and a complement can occur only when they have homologous haptophorous groups. The existence of two or more kinds of intermediary bodies in a given serum has also been demonstrated by the formation of anti-intermediary bodies. If a hæmolytic serum be injected at intervals into an animal there may

be obtained from that animal a serum which contains an anti-intermediary body, but its anti-action is not manifest toward all intermediary bodies, and may show itself only when brought in contact with that intermediary body by means of which the antihæmolytic serum has been obtained, and it is in this sense only that specific anti-intermediary bodies are known. A serum containing an anti-intermediary body prevents the action of a hæmolytic serum on the corpuscle in case that the action results from its own specific intermediary body. The action of anti-intermediary bodies consists in preventing the union between the cytophil groups and the receptors of the cell. It is altogether possible that intermediary bodies possessing different cytophil groups may have the same complementophil groups, or bodies with like cytophil groups may have different complementophil groups, and it is still possible that there may be intermediary bodies possessed of only one cytophil group, and having three or more complementophil groups. Each complement is supposed to be possessed of a haptophorous group by virtue of which it effects a combination with the intermediary body and a zymotoxic group by virtue of which it destroys the corpuscle. Ehrlich has demonstrated the close relationship between the complement among the hæmolytic factors and the bacterial toxins, inasmuch as he has proved the existence of complementoids corresponding to the toxoids. We have already learned that many of the complements are deprived of their poisonous action by a heat of 56°, and Ehrlich has shown that this apparent destruction of the complement by heat consists in destroying only the zymotoxic group. If an animal be immunized with a hæmolytic serum which has been rendered inactive by heat, there is formed in this animal not only an anti-intermediary body, but also an anti-complement. This is analogous to the production of antitoxin by treating animals with toxoids, and the anticomplement produced in this way may be quite as potent as that obtained by immunizing an animal with an unheated or active hæmolytic serum, just as a highly active antitoxin may be obtained by treating an animal with a relatively harmless toxoid. An anticomplement prevents the action of its specific complement by rendering it impossible for the latter to combine with the intermediary body. It is also probable that complements, like intermediary bodies, vary in the number of haptophorous groups which they possess. If an intermediary body be possessed of two complementophil groups it may combine with two monohaptophorous complements or one dihaptophorous complement.

It should be stated that the hæmolytic action of specific sera is explained by Bordet somewhat differently from the explanation proposed by Ehrlich. Ehrlich's intermediary body is designated by Bordet as the sensitizer (*substance sensibilitrice*), and its function is believed to

be that of rendering impressionable globules sensitive to the action of the toxic body, which Ehrlich designates as complement, and Bordet calls alexin. The contention of Ehrlich is that the combination between the corpuscles and the intermediary body is a chemical one, while Bordet explains the action of his sensitizer on physical grounds. Bordet also has prepared antisensitizers and antialexins by immunizing animals to hæmolytic sera.

Von Dungern scraped the ciliated epithelial cells from the trachea of an ox immediately after death, taking care to avoid mixture with red blood corpuscles or connective tissue, suspended these cells in physiological salt solution, and injected them into the peritoneal cavities of guinea-pigs. From time to time some of the injected cells were removed and examined microscopically. The first change observed was one of form, in which the cells were found to be rolled up like balls, but were still capable of moving through the fluid. Upon repeating this in the same animal for a number of times he found that the readiness with which the epithelial cells were destroyed rapidly increased, and from animals thus immunized to ciliated epithelium he obtained a serum which *in vitro* dissolved similar cells. The substance present in the blood serum of an animal which has this solvent action upon epithelial cells is known as epitheliolysin. Lindeman made an emulsion of the kidney substance of a rabbit and injected this into the peritoneal cavity of a guinea-pig. From the latter animal he obtained a serum which injected intravenously into rabbits caused rapid disintegration of the kidneys. The serum of animals treated with emulsions of kidney is said to be nephrolytic, and the specific toxin contained in such serum is known as nephrolysin. Landsteiner, Metchnikoff, Moxter, and Metalnikoff have treated animals intraperitoneally with suspensions of spermatozoa from diverse sources and have obtained from the animals thus treated sera which have a spermatoxic action, but up to the present time no spermatolysin has been found. Metalnikoff has found that autospermatoxins may be produced. If a guinea-pig be treated either intraperitoneally or subcutaneously with the spermatozoa of another guinea-pig, the serum of the treated animal is toxic for the spermatozoa of both. This autotoxicity may be increased by repeating the injections and there may be obtained a serum, ten drops of which added to the spermatic fluid of either animal, causes complete immobilization of the spermatozoa within three or four minutes. This autotoxin conforms to the general laws of the cytotoxins. It loses its toxic property when heated to 55° and is easily regenerated on the addition of the serum of a normal guinea-pig. There are some very interesting points in connection with this subject. For instance, a guinea-pig whose blood contains a toxin which is markedly toxic to its own spermatozoa *in vitro* has

spermatozoa which are quite as motile as those of a normal animal, and which when introduced into physiological salt solution live for a long time. However, if these spermatozoa be placed in the serum of a normal guinea-pig they die within from ten to twenty minutes, while the spermatozoa of a normal guinea-pig live in the serum of another normal animal for many hours. This is explained by stating that these spermatozoa have been acted upon by the sensitizer circulating in the blood of the guinea-pig, but they are not killed by the autotoxin of the animal because the blood does not contain a free alexin, inasmuch as this factor exists only in the interior of the leucocytes. This is offered as an explanation why autotoxins may be active *in vitro*, but inactive *in vivo*. The cellular elements are destroyed in the serum *in vitro* and then both the sensitizer and the alexin are set free, while in the living organism the alexins are held within the leucocytes and the sensitizer, although freely circulating in the blood, is unable in and of itself to destroy the spermatozoa.

Metchnikoff has inoculated animals with emulsions of the spleen and mesenteric glands and in this way has obtained a serum which agglutinates and dissolves the white blood corpuscles. The active agent in sera of this kind is known as a leucolysin.

The Agglutinins.

As early as 1889 Charrin and Roger observed that the bacillus pyocyaneus behaved peculiarly when placed in the serum of an animal which had been immunized to this organism. In the serum of a normal rabbit this germ grows as it does in beef tea, forming an opaque culture, while in the serum of an immunized rabbit these microbes form floating floccules, which soon subside, leaving a clear supernatant fluid. In studying immunity, Metchnikoff found that the vibrio bearing his own name behaves in a manner similar to that observed by Charrin and Roger. In 1893 Issaeff observed like phenomena when the pneumococcus was placed in its homologous serum. However, the importance of the phenomenon of agglutination may be said to be due to the classical research of Gruber and Durham, reported in 1896. These investigators found that when the cholera or typhoid bacillus is taken from growth on agar and suspended in its homologous serum, the bacteria lose their motility and form clumps or masses. They attributed these phenomena to the presence of specific substances in the serum, for which they proposed the term agglutinins, and suggested that the phenomenon might be designated as that of agglutination. A few months after the publication of the last-mentioned paper, Widal reported the successful application of the phenomenon of agglutination in the diagnosis of typhoid fever, and among

clinicians it is generally known as the "Widal reaction." It must be evident that in such a reaction as that observed in agglutination, at least two factors are concerned. One of these, which we designate the agglutinin, is found in the serum, while the other, which may be denominated the agglutinable substance, is furnished by the bacterial culture, while the product which results from the reaction between these bodies may be known as the agglutinate. First we will confine our attention to the agglutinins. The normal serum of certain animals is capable of manifesting a slight agglutinating action upon certain bacteria, notably the colon bacillus and the bacillus of Eberth, and it is still a question whether the agglutinating action manifested in the serum of immunized animals or that of persons sick with typhoid fever is due to an exaggeration of a normal property or is caused by the presence of a new substance. Agglutinins are found not only in the blood but in other fluids of the body as well. Compared with the agglutinating property of the blood, that of the urine is always feeble, and varies from hour to hour without any explainable cause. This renders the use of this secretion in place of blood serum impracticable. Tears often agglutinate, but the action of this secretion is also variable, and tears obtained by artificial stimulation are generally devoid of this property. The agglutinins are fairly stable bodies and many of them may be heated to 140° without destruction, but that of the typhoid bacillus is apparently destroyed at a temperature of 115°. Typhoid serum may be treated with formalin and kept quite indefinitely without loss of its agglutinating properties. However, the use of germicides is not necessary in order to have a serum retain its agglutinating action. A typhoid serum may be used as a culture medium for the germs of cholera, anthrax, diphtheria, or the ordinary putrefactive bacteria without apparent diminution in its agglutinating property. Dilute mineral acids decrease the agglutinating property of typhoid sera, but when the acid has been added in dilute form and has not remained long in contact with the serum, partial restoration may be induced by neutralization with alkali. Acetic acid has a like but less marked effect. Caustic alkalies act similarly to acids. The digestive ferments have no effect upon the agglutinins. Filtration of blood serum through porcelain removes the greater part of the agglutinin. Saturation of typhoid serum with magnesium sulphate leads to precipitation of the greater part or all of the agglutinin. When the precipitate thus obtained is dissolved in water it will be found that its action has not been destroyed by precipitation. Complete saturation with sodium chloride and half saturation with ammonium sulphate have practically the same effect. It may be concluded from these reactions that agglutinin is one of the globulins or albumins existing in the blood, but this conclusion does not necessarily follow.

It is possible that the agglutinin is carried down mechanically, as happens to certain ferments and toxins when albuminous solutions are treated with neutral salts. On the other hand, the fact that the agglutinating action has been secured with urine in which no albumin or globulin could be detected has led some to believe that the agglutinins belong to neither of these bodies, but this conclusion is not justifiable. Prolonged contact with absolute alcohol destroys agglutinin. The agglutinating action of blood plasm obtained by the addition of oxalate of potassium to the blood is more marked than that of the serum of the same blood.

The nature of the agglutinable substance is not known. Nicolle reported at one time that the agglutinable substance is soluble in absolute alcohol and ether. Had this statement been confirmed the separation of this body from the proteids would have proved to be comparatively easy, but subsequent researches have shown that Nicolle fell into error on this point. The fact that typhoid cultures, the germs of which have been destroyed by the use of disinfectants or the application of heat, still agglutinate homologous sera demonstates that the agglutinable substance is not destroyed when these organisms are deprived of life. Several hypotheses have been proposed concerning the phenomenon of agglutination. It was suggested by Gruber that there must be something in the immune serum which profoundly alters its homologous bacterium and he believed that this alteration consists, in part at least, of an increased viscosity of the cell membrane of the bacterium. The production of an adhesive substance is supposed to be the chief factor in the agglutination or clumping of the bacterial cells, and when two or more germs are brought together, either by active or passive movements, they adhere one to the other, lose their individual motility, and form small masses, which gradually subside in the culture medium. Nicolle offers a theory which provides for a precipitate formed between the agglutinin contained in the serum and the agglutinable substance which diffuses from the bacterial cell. The agglutinable substance is supposed to be most abundant in the cell membrane, and by the union of the agglutinin and the agglutinable substance small coagula are formed and surround the bacterial cells.

Food Poisoning (Bromatotoxismus).

The most important contribution that has been made within the last four years to the subject of food poisoning relates to the discovery by Van Ermengem of a bacillus in poisonous meat and the subsequent investigation of the toxin of this germ. The ham which proved to be poisonous in this case seemed to be perfectly normal. The affected persons showed little or no evidence of gastrointestinal irritation, but

nervous symptoms were prominent and consisted of diplopia, mydriasis, ptosis, aphagia, aphonia, and anuria. There were two deaths. Other portions of the carcass of the animal from which this ham came were eaten without harm, and it was observed that the poisonous ham was the only part of the meat which was completely submerged in the brine, and it was inferred from this that the harmful germ would be found to be strictly anaërobic. This proved to be correct, and, furthermore, it was found that the bacillus produces a toxin almost as poisonous as tetanotoxin, inasmuch as it requires only 0.0005 mgm. to kill a rabbit in twenty-four hours. This microorganism has been designated as bacillus botulinus, and its poisonous substance as botulismustoxin. According to the experiments of Marinesco, when this toxin is administered by mouth to cats it causes mydriasis, partial paralysis, aphonia, impossibility of deglutition, and muscular weakness. The same observer ascertained that the lesions induced by this toxin are confined very largely to the cells of the gray matter of the cord. After the administration of small doses the only abnormal appearance consists of a rarefaction of the chromatophil elements, while under the influence of larger amounts the granules of Nissl undergo a more or less marked disintegration or chromatolysis. When fatal doses are administered many cells will be found to be completely destroyed. Brieger and Boer have prepared this toxin by their method of precipitation with chloride of zinc, but have been unable to obtain it in a pure state. Apparently it belongs to the albumoses, and Kempner has immunized animals to it and has obtained a specific antitoxin. The last-mentioned observer, together with Pollac, has confirmed the microscopical studies of Marinesco, and has demonstrated that under the influence of the antitoxin, cells which have been injured by the toxin show visible evidences of repair.

McClymonds and the writer, in continuing the studies of poisonous cheese, examined sixty-five samples from as many different manufacturers. Of these, forty-nine were what is ordinarily known as American green cheese, and were made in Michigan, Wisconsin, Illinois, New York, and Ontario. Eight of the forty-nine samples were sent to the laboratory because persons eating them had suffered from vomiting, nausea, and purging, while the other samples had not been suspected of being injurious. All of the forty-nine samples furnished cultures which killed white rats, guinea-pigs, and rabbits. The toxicogenic germ in all of these samples belongs to the colon group, and apparently the effect of this cheese upon the consumer is largely dependent upon the amount and virulence of the germ substance present in the cheese. Cooley and the writer continued this work and have shown that the colon toxin is contained in the germ cell from which it does not, at least under ordinary conditions, diffuse into the cheese, and

that the toxicity of a given sample may be measured by the number of colon germs present, bearing in mind always that these germs may vary in virulence in different samples, and even in different parts of the same cheese.

PROTOZOA.

BY

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THE perfected methods of bacteriological investigation having failed to demonstrate bacteria in association with many diseases, the course and spread of which suggest the presence of a living contagium, the possibility arises that they are caused by protozoa, and in many instances microorganisms supposed to belong to the animal kingdom have been described. The methods available for the study of protozoa being more limited than those applicable to bacteria, the difficulties of their demonstration are greater, and moreover a variety of minute structures, altered cells, and parts of cells may be mistaken for animal parasites. Well-established types of microorganisms, pathogenic for man, are Amœba coli and the malarial parasites. These organisms have at different periods of their development a constantly recurring structure resembling that of other protozoan species and are identified as living parasites by their characteristic movements which only remotely resemble those of cell constituents of the body. Among lower animals a familiar type of animal parasite is Coccidium oviforme of rabbits. In a considerable variety of diseases there have been found minute bodies supposed to resemble amœbæ or coccidia or some stage of the malarial parasite, and demonstrable by direct examination of fresh tissues or exudates or by staining methods applied to the fixed tissues. In many instances these observations have not been confirmed and have attracted so little attention that they deserve slight consideration.

Many such bodies observed in the blood have been thought to be the cause of the disease with which they have been associated. During the eruptive stage of measles, Doehle found minute refractive bodies exhibiting, as he thought, amœboid movements, and after the appearance of the eruption noted free in the plasma bodies upon which he thought flagella could be demonstrated by methods of staining. He later found both amœboid and flagellate bodies in the blood

and in the contents of smallpox vesicles, and in the blood of scarlet-fever patients, while in the juice expressed from syphilitic lesions he observed almost identical bodies. In pernicious anæmia Klebs found in the blood motile bodies which he believed to be hæmatozoa and later saw similar bodies in cases of influenza. In three cases of pernicious anæmia Perles found in blood examined under the microscope upon a warmed stage, small ovoid flattened bodies which presented curious active movements. In the blood from cases of typhus fever Thoinot and Calmette observed motile nodular filaments which were often attached to the red blood corpuscles. Neither Perles nor Thoinot and Calmette were fully convinced as to the parasitic nature of the bodies they described. With beriberi Fijardo has described in the red corpuscles amœba-like bodies containing pigment granules and resembling the Plasmodium malariæ, but his observations have not been confirmed. Graham has recently noted large non-pigmented amœba-like bodies within the red corpuscle in cases of dengue.

Since many of these bodies present little that is characteristic in structure their classification among any of the established protozoan groups is not possible. Minute protoplasmic particles observed either in the fresh state or in stained specimens have been interpreted as amœbæ. In the fresh blood occur a variety of appearances which suggest parasitic organisms and the great variety of changes to which the red blood corpuscle are subject when exposed to artificial conditions are well known. Within the red corpuscles, particularly after exposure to injurious influences, are formed sharply defined vacuoles of irregular shape, resembling, though much more refractive, the hyaline bodies of the malarial fevers. These vacuoles may undergo alterations of outline suggesting amœboid movement. Under certain conditions filaments resembling flagella are formed from the red corpuscle, and these doubtless are the structures described by Thoinot and Calmette in typhus fever. Free in the plasma are frequently seen minute refractive bodies smaller than blood plaques and resembling small fat droplets and characterized by an active dancing Brownian movement. These particles, described by Müller and designated hämokonien (blood dust) granules are thought by him to be a normal constituent of the blood, though their nature is unknown. They represent apparently some of the pseudoparasites found in the blood in measles, scarlet fever, smallpox, vaccina, and carcinoma.

Amœboid movement is not peculiar to the leucocytes and may occur with other cells, even those of epithelial origin; as Kruse states, observations under abnormal conditions of temperature may excite unexpected movement and produce a misleading appearance of independent vital activity. In the fresh sputum of patients suffering with whooping-cough, examined upon a warm stage, Deichler and later

Kurloff found amœboid bodies often provided with active cilia. It is not improbable that what they regarded as protozoan parasites were distorted ciliated cells which occasionally preserve their activity for a short time in the fresh sputum. It is, however, impossible to identify many of the bodies described with known cellular elements, and in the absence of confirmation it is probable that in some instances at least erroneous observations have been made.

The difficulty of establishing the parasitic nature of bodies which are identified only in hardened and stained tissue is obviously great. Unusual forms of degeneration, particularly those associated with abnormal hornification of epithelial cells, have been a frequent source of error. The inclusion of one cell, notably a polynuclear leucocyte, by another may have a similar result, while various forms of nuclear degeneration give rise to bizarre appearances which, though correctly observed, may form the basis of erroneous conclusions. With these objections in view there are nevertheless several very important diseases in association with which have been repeatedly described, often by well-known observers, pseudoparasites the identity of which cannot be summarily dismissed, since in some instances they have been found to be constantly present in the disease in question and absent in other conditions. Though their parasitic nature is denied their relationship to the disease process is established. The burden of proof is obviously upon those attempting to establish the identity of these bodies with protozoan microorganisms, but to disprove this supposition conclusively it is desirable to establish their relationship to some normal cell structure or to some form of degeneration. The pseudoparasitic bodies described in carcinoma, leukæmia, smallpox, and vaccina are worthy of detailed consideration in view of the vast importance of establishing the etiological factors concerned in the production of these diseases.

CARCINOMA.

At a time when knowledge of pathogenic microorganisms was meagre the infectious nature of cancer was vaguely discussed; but with a clear appreciation of the relationship of bacteria to various pathological processes, notably to the tumor-like formations classified as infectious granulomata, the parasitic origin of carcinoma soon suggested itself and numerous attempts were made to discover microorganisms associated with the disease. Beginning as a localized lesion, rapidly progressing, and finally disseminated as metastases throughout the body, carcinoma presents an analogy to tuberculosis and other infectious diseases which is strengthened by the occurrence of the accompanying cachexia.

In the early years of bacteriological study a variety of bacteria

isolated from new growths were described as their cause. The results of bacteriological examinations were, however, inconstant and the organisms isolated were identified with those found under many other conditions. The investigations of Senger, Baumgarten, and Rosenthal have shown that the presence of bacteria in tumors may be regarded as accidental, the result of secondary invasion, and an accompaniment of degeneration, ulceration, and inflammation of the tumor tissue.

Less readily proven or disproven is the causal relationship of protozoa to the disease, and numerous bodies found in carcinomatous tissue have been regarded as protozoan parasites. Presenting the appearance of amœbæ they have been assigned to the order Rhizopoda, or found within the bodies of cells and apparently multiplying by a process of segmentation or sporulation they have been designated Sporozoa. Many of the bodies described have resembled coccidia, and Coccidium oviforme, the so-called psorosperm of rabbits, which develops within epithelial cells of the liver and intestine, has been regarded as their analogue. Metchnikoff cites the objection of Cohnheim to a parasitic theory of malignant neoplasms. "Never," Cohnheim says, "has any epidemic or endemic of true tumors been observed. Further it has never been possible to prove the transmission of a tumor from one individual to another. Never has a surgeon infected himself with a tumor during an operation, neither has a man ever been known to have contracted cancer of the penis in consequence of his wife suffering from uterine cancer. And how many fruitless experiments have been made with the object of transmitting tumors from man to animals or from one individual of the same species to another?" Metchnikoff points out that our ideas of infection have changed. Tuberculosis is apparently not more endemic nor epidemic in character than cancer, and the absence of contagion is not proof that the affection is not caused by a microorganism; for, as exemplified by the malarial parasites of man and the coccidia of rabbits, an infectious disease does not necessarily spread by the direct transmission of a parasite from one individual to another, since it may be essential that the organism undergo a variety of changes outside the body before it is prepared to infect a second host.

In a few instances cell proliferation resembling that of benign tumors is produced in lower animals by the invasion of protozoa, but in most instances the analogy is slight. Proliferation of nuclei without cell division is caused by certain intracellular myxosporidia (Nosema ovoideum and Nosema bryzoides) parasitic in fish; and in the barbel proliferation of muscle fibres is caused by Myxobolus pfeifferi, but the infected fibres are not those that proliferate, so that the process may be regeneration. In rabbits proliferation of epithelial cells

infected with Coccidium oviforme occurs in the bile ducts and the resulting lesion may resemble a benign adenoma.

Virchow in 1851 described and pictured within the cells of carcinomata bodies which have been since regarded as protozoan parasites. He attributed these structures to a process of endogenous cell formation, since within round cavities sharply defined by a double-contoured wall was found at times homogeneous hyaline material, at times nuclei or even entire cells; one cell, he thought, was formed within another.

Structures believed to be animal parasites inhabiting the cells of carcinomata were first described by L. Pfeiffer in 1888, and subsequently in rapid succession a great variety of structures have been noted, although few who have contributed to the subject have been able to define clearly the relationship of their organisms to those previously observed. Pfeiffer states that in the metastases from a carcinoma of the leg occurring in a girl fifteen years of age, he found bodies resembling the parasite of pebrine disease in silkworms. A variety of forms, some amœboid, others resembling spore cysts, are mentioned by him, but are not described in detail. Similar bodies were later found in a sarcoma of the breast, in a carcinoma beginning as a wart upon the leg, and in a melanotic sarcoma, but from his meagre mention of a considerable variety of structures no judgment as to their nature can be formed. A provisional grouping of some of the more important bodies since described may be adopted for the sake of convenience, but no accurate classification is possible.

Coccidia-like Bodies in Squamous-cell Epitheliomata.—In carcinomata of epithelial origin affecting the jaw, Mallassez and Albarran found intracellular bodies which they believed to be psorosperms or coccidia, and their opinion was confirmed by the zoologist Balbiani. These bodies were round or somewhat oval and contained a round, centrally placed nucleus in which was often seen a distinct nucleolus. Many were surrounded by a hyaline membrane of variable thickness, closely applied to the cell body or separated from it by a narrow space. Others were not encapsulated and were often somewhat irregular in shape.

Darier about the same time described intracellular coccidia-like bodies usually surrounded by a well-defined capsule, in the skin disease to which he gave the name psorospermosis follicularis vegetans. The epithelial cells forming the upper part of the hair follicles undergo in this disease active proliferation, which is accompanied by an abnormal process of keratinization, and within these altered cells are found the coccidia-like bodies. Darier and later Wickham found the same bodies in Paget's disease of the breast, a condition characterized by proliferation of the epithelium of the nipple. The disease frequently terminates as cancer, into which it is believed to pass by gradual process of transition. Vincent subsequently found coccidia-like structures

in squamous-cell carcinomata of the tongue, lips, and nose, and Hacke, Unna, and others have found them in tumors arising from the Malpighian layers of the skin. The so-called molluscum corpuscles believed by Neisser, Pfeiffer, and others to be protozoan parasites causing molluscum contagiosum resemble the psorosperms of Darier.

The various lesions with which these bodies are associated have in common an active proliferation of the epithelial cells followed by an abnormal process of keratinization. Buzzi, Boeck, Petersen, and Gilchrist regard them as products of degeneration. Boeck and Petersen in cases of Darier's disease have found transitions to normal cells, and tracing their development have shown that an abnormal process of keratinization occurs in young epithelial cells in consequence of which refractive material resistant to stains is formed at the periphery of the cell, or both at the periphery and immediately about the nucleus, while the intervening protoplasm contains the keratohyaline granules, observed in normal hornifying cells. By serial sections Petersen demonstrated the intracellular position of the parasite to be only apparent. The altered cells undergoing an earlier hornification withstand the pressure of the adjacent softer growing cells, one of which assumes a half-moon shape and at first partially, later completely, surrounds it. Petersen found the same abnormal process in other skin diseases associated with active proliferation and keratinization of squamous epithelium, and Fabre-Domergue, Pianese, and others have shown that the formation of coccidia-like bodies in squamous-cell epitheliomata is a similar process of abnormal keratinization, and have traced the various stages of their development.

Coccidia-like Bodies in Carcinomata of Glandular Origin.—A large number of observers have described structures believed to be parasites in the cells of carcinomata having their origin in glandular structures or in organs provided with columnar or cubical epithelium, and in a few instances similar bodies have been observed in carcinomata arising from the skin and even in sarcomata. They appear, however, to be most numerous and characteristic in malignant neoplasms of glandular origin. Such structures have been usually demonstrated in tissue hardened with corrosive sublimate or with some fluid containing osmic acid, but they are observable after the use of almost all fixing agents. Thoma in 1889 described structures resembling small monocellular organisms 14 or 15 μ in diameter, situated within the nucleus of the cancer cell. They possess cell protoplasm, a nucleus, and sometimes a nucleolus. As many as four or six may be present within the same nucleus, which, losing its capacity for staining, is replaced by vacuole-like bodies which contain chromatic bodies of varying size. Sjöbring observed similar bodies in a carcinoma of the breast, and finding them sometimes in the nucleus, sometimes in the cell protoplasm, came to

the conclusion that the organism, which resembled the parasite of pebrine disease in silkworms, began its development in the nucleus, but subsequently made its way into the cell body. The full-grown parasite became, he thought, encapsulated and underwent segmentation to form spores.

In a small proportion of the carcinomata which he examined Foà found within the cell body, but not in the nucleus, rounded structures of variable size, containing a central nuclear body, and occasionally was able to observe an appearance suggesting segmentation. Bodies observed by Soudakewitch were identified with those of Foà, and both writers describe and picture a variety of structures in many of which radiating lines pass inward from the periphery toward the central nuclear particle.

Similar bodies have been described by Podvyssotski and Savchenko in a variety of carcinomata arising from the skin, testicle, breast, and stomach. They occur within the cell protoplasm and several are occasionally observed in the same cell. These writers have described what they believe to be a reproductive process resulting in the formation of sickle-shaped embryos within a cyst, but the irregularity in shape and size presented by the structures which they picture is sufficient, according to Metchnikoff, to exclude the possibility that they represent the falciform embryos of sporozoa. Extracellular bodies believed by Podvyssotski and Savchenko to be conglomerate masses of parasites show little resemblance to the isolated forms, and in their drawing have the appearance of hyperchromatic nuclei. The diverse bodies which they describe are more abundant in medullary cancers, and the softer the cancer the more active the growth, and the greater the tendency to degeneration the more numerous are the cell inclusions. Since they are found in some but not in the majority of those cells, nuclei of which give evidence of karyokinetic division, the authors reach the surprising conclusion that the parasites they have described are not the cause of the tumor but are secondary invaders which find suitable conditions for development in the carcinomatous tissue.

Bodies observed by Ruffer and Walker and by Ruffer and Plimmer in tissue fixed with osmic acid and stained by Biondi's method are doubtless identical with some of those just mentioned. Though the so-called parasites are most numerous near the growing edge of the tumor, the infected cells hardly ever show evidence of division, whereas numerous karyokinetic figures are seen near by, so that the observers mentioned think the parasite excites the division of neighboring cells, while it causes its host to perish. Ruffer and Plimmer limited their study to carcinomata of the breast, since they believe that different varieties of parasites occur in different forms of new growth. Agree-

ing with Sjöbring they think that the parasite begins its life history in the nucleus of the cell and later is extruded into the cell protoplasm. Plimmer continuing these studies found in 1,130 of 1,278 cancers pseudoparasites which he regards provisionally as protozoa, though he thinks the possibility that they are blastomycetes cannot be excluded. He carefully describes the structures he has observed, and though they are apparently identical with those found by Soudakevitch and others, English writers in view of his careful study have designated them Plimmer's bodies.

These intracellular structures or bodies of Plimmer were observable in fresh material as well as in tissues fixed by solutions of osmic acid and corrosive sublimate and stained by the Ehrlich-Biondi mixture, by thionin or by hæmatoxylin. They are round bodies varying from 4 to 40 μ in diameter, or may be even larger. There is a central part which for convenience may be called a nucleus, though according to Plimmer it does not react to stains as does the nucleus of the cancer cell. The substance about the nucleus is usually homogeneous, but in the larger bodies in fixed specimens often exhibits radiating striations. Surrounding the body is a well-defined capsule which stains conspicuously. Multiplication takes place by direct division into two individuals, the nucleus first dividing. This process may be very rapidly repeated so that within a single cell as many as sixty-four parasites may be found. Plimmer observed a second form of division or segmentation by which a single individual divides into a considerable number of small bodies, but there is no resemblance to a sporocyst and the formation of crescentic or falciform reproductive bodies described by Podvyssotski and Savchenko was never seen.

A review of the descriptions given by the writers previously cited leaves little doubt that identical intracellular structures have been studied by a considerable number of observers, including Sjöbring, Soudakevitch, Podvyssotski, Savchenko, Ruffer, Walker, and Plimmer. Among the great variety of pseudo-parasites described by these and other writers are included structures which, occurring in parts of the tumor undergoing degeneration, are evidently the result of degenerative changes in the nucleus or in the body of the cancer cell, and adherents of the protozoan origin of the disease citing the work of their fellows freely offer this suggestion. The intranuclear bodies described by Thoma and Sjöbring have attracted less attention from more recent observers and agree closely with vacuole-like degenerative changes described by Ribbert, Pianese, and others. The bodies which Plimmer and Savchenko have very carefully described have apparently been observed, along with other structures, by all the writers mentioned, and since they are present in at least a large proportion of all carcinomata their significance is of great importance. Plimmer was able to

examine these bodies in the fresh state, but the absence of amœboid or other movements is not an objection to their parasitic nature, since no motility is observed with many encapsulated protozoa even in their earliest stage of development. An important factor in demonstrating their parasitic nature is the observation of a process of multiplication. Reproduction of these intracellular bodies has not been clearly demonstrated, and various writers have described dissimilar processes. Soudakevitch, Podvyssotski, and Savchenko describe, as before mentioned, the formation of crescentic or falciform reproductive bodies which Metchnikoff believes to be particles of nuclear chromatin, although he regards as protozoa other inclusions they describe. Plimmer thinks that reproduction is by direct division or more rarely by a process of segmentation without the formation of falciform embryos.

Those who maintain the parasitic nature of the bodies described are not agreed as to their relation to other microorganisms. The majority of writers, among whom is Metchnikoff, have emphasized a supposed resemblance to coccidia and have assigned them to the class Sporozoa. Sjöbring, basing his conclusions upon the results of attempted cultivation, regards them as rhizopods. Plimmer is not able to reach a definite conclusion, but thinks that it is expedient to regard the bodies as protozoa, though they present many similarities to a wholly different group of microorganisms, the yeasts or blastomycetes, belonging to the vegetable kingdom.

A number of Italian observers have obtained from malignant growths cultures of blastomycetes, and conclude that they are the exciting cause. Sanfelice has maintained that the cell inclusions observed by Plimmer and others are yeasts, and claims that they do not differ from those found in the tissues after inoculation of yeasts into animals, but careful comparison by Busse and by Nichols of the bodies of carcinoma with well-established blastomycetes in human lesions or in the tissue of inoculated animals has shown no close resemblance.

Those writers who deny the parasitic nature of the bodies in question claim that they are the result of degenerative changes in the protoplasm or in the nucleus of the cells. A painstaking study of the degenerative changes which occur in the cells of carcinomata has been made by Pianese, whose monograph contains an exhaustive survey of the previously described protozoa-like bodies of cancer. He has devised a large number of special methods of staining, and by their use has studied the degenerations to which nuclei of cancer cells are subject and has compared the intracellular bodies of cancer with various forms of mucoid, hyaline, colloid, and amyloid degeneration. He concludes that all the protozoa which have been described in carcinomata are nothing more than altered products, either of the protoplasm or of the nucleus, or of both protoplasm and nucleus, and in many instances are

the products of an atypical process of secretion. He thinks that globules of mucoid material formed within the cell protoplasm may undergo such alterations that they assume the appearance of the peculiar bodies which are observed in almost all carcinomata derived from glandular organs.*

Borrel has offered a new explanation of these structures of which the regularity of form suggests so strongly parasitic bodies and so little any known variety of degeneration. He thinks that they represent the attraction sphere of the cancer cell. They present a close resemblance to the attraction sphere and its centrosomes which are readily observable in the testicle of the guinea-pig within cells about to form spermatozoa. By appropriate staining methods the attraction sphere of the cancer cell is demonstrable at a time when it presents no resemblance to protozoan organisms, but the appearance so frequently described is produced by the formation of a vacuole-like space about one or more of the contained centrosomes.

Other So-called Protozoa of Cancer.—Under the name Rhodocephalus carcinomatosus Korotneff has described in epitheliomata what he believes to be protozoan organisms belonging to the order Gregarinæ. The developed parasite occurs in two wholly different forms: (*a*) an organism resembling a monocystid gregarine with an enlarged head containing a nucleus, and a tail-like body several times the length of the carcinoma cells by which it is surrounded, and (*b*) an amœba-like body which is capable of reproduction. The latter develops within or between the cells and may form about itself a capsule or may remain unencapsulated. Within its substance are formed one or more reproductive bodies, some oval and naked, others falciform and encapsulated. The reproductive bodies having made their way into new cells develop to form either the gregarine-like or the amœboid body. The observations of Korotneff, whose organism has no analogue among protozoan species, have found no confirmation, though the amœba-like bodies are doubtless, in part at least, structures previously described by writers already mentioned. Von Leyden has observed large amœboid bodies in the ascitic fluid of two patients suffering with carcinoma, and Schaudinn has given them the name Leydenia gemmipara. Pfeiffer thinks that many of the cells usually thought to be of epithelial origin or derived from the stroma, as well as many small cells described as emigrated leucocytes are indeed parasites, while Adamkiewicz has recently advanced the opinion that all cancer cells are parasites and the cancer is not a tissue but a conglomerate of numberless organisms.

* The hypothesis that these cell inclusions represent altered products of secretion has recently received support from Greenough, who has been able to demonstrate similar structures in benign adenomata and even in the altered cells of the mammary gland affected with chronic inflammation.

In the blood of cancer patients Kahane found small bodies morphologically indistinguishable from blood plaquelets, but characterized by the possession of active movement explicable only upon the supposition that they possess flagella. Similar bodies, at times showing amœboid movement, were found in the red blood corpuscles, and he describes a variety of forms which occur in the plasma, in the red blood corpuscles, and occasionally within the cancer cells. Subsequent observers have not confirmed these observations, though the method employed by Kahane was mere examination of fresh material. Minute refractive bodies with active Brownian movements are not infrequently seen in specimens of fresh blood and are not characteristic of cancer, while the red blood corpuscles are susceptible to changes which may be wrongly interpreted. Recently Gaylord has again described in the blood and in ascitic fluid from cases of carcinoma implicating the peritoneum bodies similar to those observed by Kahane. In blood-tinged ascitic fluid obtained from a colloid adenocarcinoma of the peritoneum were found homogeneous spherical bodies 2 to 10 μ in diameter and of pale yellowish-green color. They resemble fat droplets and are undissolved by ether and potassium hydroxide and do not stain with osmic acid, though like fat they assume a red color when treated with the dye Sudan iii. These bodies Gaylord finds are constantly present in the organs of those dying of carcinoma and of sarcoma as well, while, when cachexia is present, they may be found in the peripheral blood during life.

The foregoing account shows what diversity exists among the bodies which have been interpreted as protozoa causing malignant growths. None of these so-called parasites present the regularity of size and structure found among the parasitic protozoa the identity of which is well established. There has been much diversity of opinion concerning the method by which they multiply in the tissues, and the reproductive bodies which have been described do not present the uniformity of shape and size which occurs among the sporozoa. Many adherents of the so-called parasitic theory of cancer have recognized the impossibility of demonstrating the parasitic nature of these cell inclusions by the mere study of hardened tissues, and numerous attempts have been made to cultivate them in artificial media.

Cultivation and Inoculation.—Several observers believe that they have been able to cultivate protozoan microorganisms from neoplasms and even to produce tumors by inoculating animals with their cultures. In a medium containing glucose, tartaric acid, and an infusion of cancer tissue Plimmer obtained from carcinomata an abundant growth which developed under anaërobic conditions and less luxuriantly aërobically. The growth which developed on potato as well as upon his special medium consisted of round bodies with a central

staining particle and often provided with a capsule. They resembled the bodies which were observed in hardened tissues. Since they reproduced by a process of budding it is probable that Plimmer obtained in his cultures some species of blastomycetes. By injecting these cultures into animals in a few instances he produced tumor-like nodules which were certainly not carcinomata, since Plimmer states they were composed of endothelial cells.

By inoculating with material from carcinomata and sarcomata a strongly alkalinized medium composed of potassium soap derived from human fat, together with peptone, gelatin, and glucose, Sjöbring observed a great variety of forms which developed as well at room temperature as after incubation at 37°. Their diversity was so great that he finds a description and classification of them impossible and comes to the conclusion that there exists a considerable variety of different species. Very bizarre structures, some amœboid, some encysted, some of curious spiral shape are pictured, but their relation to one another is wholly inexplicable. Amœboid movement is described, and Sjöbring regards these bodies as rhizopods. By inoculating such material into eight mice he obtained, as he believes, epithelial tumors in four cases, but the descriptions of his results are little more convincing than the character of his cultures.

Gaylord believes that he has been able to cultivate the bodies which he found associated with malignant growths. In ascitic fluid containing these bodies, kept at body temperature and examined from day to day, they were believed to increase in size, lose their green color, and present long projections or pseudopods. The protoplasm appeared granular and a delicate nucleus could be seen. Ultimately the larger forms of the organism seemed to be transformed into what appeared to be large sacs containing highly refractive granules and small spherical bodies similar to those found in the original fluid. It does not appear improbable that the appearances described may result from maceration of cells or parts of cells contained in the original fluid. At the end of two weeks several cubic centimetres of the incubated material containing the spore-like bodies were injected into the jugular vein of a guinea-pig. The animal was killed after fifty days and the lungs were found to contain minute white nodules, which are described as beginning foci of adenocarcinoma, though the photograph accompanying his description is not convincing. Other animals inoculated with the original material and with that from the guinea-pig just mentioned developed no tumor masses, but minute fat-like bodies, similar to those previously observed in association with carcinoma, were numerous in their blood and organs.

Using the staining methods employed by Plimmer, Gaylord has found in both carcinomata and sarcomata the characteristic bodies

described by that writer, and identified the smallest of them with the fat-like particles resembling cocci found in fresh material. In hardened tissues from malignant growths, and indeed in uninvaded lymph glands, he likewise found the hyaline globules described by Russell and designated on account of their affinity for acid fuchsin, fuchsin bodies. Transitional stages between Plimmer's bodies and fuchsin bodies are described, and Gaylord regards the latter as one form of his parasite. On the other hand, the so-called fuchsin bodies, which were thought by Russell to be blastomycetes, have been repeatedly observed in many lesions other than malignant growths, and are almost universally believed to be the result of a hyaline degeneration of cell protoplasm.

The study of hardened and stained tissues has demonstrated the occurrence of peculiar bodies, which can be almost constantly found when sought by appropriate methods. Though they resemble in some respects protozoan microorganisms, various stages of their development and multiplication have received no adequate demonstration. The study of fresh material has added little to the knowledge of these structures, and the results of experimental cultivation and inoculation experiments are such as to afford no convincing evidence of their parasitic nature.

VACCINA AND SMALLPOX.

In 1877 Van der Loeff found in lymph from the vesicles of vaccina numerous amœboid structures which he described as rhizopods, the cause of vaccina, and subsequently observed the same bodies in the fresh vesicles of smallpox. Pfeiffer a few months later described protozoa-like bodies in the pock of various mammals and of man. The lesion first manifests itself by swelling and necrosis of the cells forming the Malpighian layer of the epidermis. The parasite, according to Pfeiffer, makes its appearance in these cells, and their destruction is the result of its presence. He designates it Monocystis epithelialis and states that it resembles the coccidia. It occurs within the epithelial cell as a round or oval nucleated body larger than a red blood corpuscle. It forms about itself a capsule within which is seen a second cyst-like membrane, while the remaining protoplasm gives rise to spores which appear as minute round bodies resembling micrococci. At first these bodies, Pfeiffer states, are found only in the cells, but after the third until the sixth day following inoculation they are found free in the serum, but rapidly disappear after invasion of bacteria and the formation of a pustule. The lymph used for vaccination contains both spores and organisms developed from them, so that in lymph preserved in glycerin are found spores indistinguishable from micrococci and bodies which on the warm stage exhibit active

amœboid movements. The amœboid bodies develop presumably from the spores, but the process was not observed.

Guarnieri, confirming in part the observations of Pfeiffer, has very clearly described the bodies which occur both in the pock of variola and in the lesion which follows vaccination with animal lymph. They vary in size from that of a micrococcus to that of the nucleus of an epithelial cell, and in fresh material appear as refractive bodies readily distinguished in the protoplasm of the cell. They are somewhat irregular in outline and are often provided with blunt projections, as though capable of amœboid movement. They do not possess capsules as Pfeiffer described, but in tissue that is hardened and stained are seen to lie within a clear space in the protoplasm of the cell in contact with the nucleus which is indented and distorted. Believing these structures to be protozoan microorganisms Guarnieri has given them the name Cortyces variolæ. They are doubtless identical with the bodies described by Weigert in 1874, and believed by him to be the results of budding of the cell nucleus.

An important addition to the knowledge of these bodies was made by Guarnieri, who found that they occurred plentifully in the epithelial cells of the cornea after inoculation with vaccine virus. His experiments have been abundantly confirmed, and the corneal inoculation of animals has afforded a very convenient method for their study. Gorini has suggested that inoculation of the cornea may be employed as a test of the purity and activity of vaccine virus. After inoculation a clouded spot about one millimetre across, surrounded by very minute nodules, appears upon the cornea. The process affects only the epithelial cells, which undergo active multiplication. Within them are seen round nucleated bodies lying beside the nucleus of the cell. These bodies can be seen in isolated corneal cells examined while fresh upon the warm stage. Pfeiffer claims that they exhibit amœboid movement. Leucocytes do not wander into the affected area until after about forty-eight hours, and bacteria are not demonstrable until a later period. Hückel has made a very careful study of the intracellular bodies found in the hardened corneal tissue after staining by a variety of methods. Their central part is stained by nuclear dyes, while the peripheral part, which often contains small granules, takes up protoplasmic stains.

Intraepithelial bodies have been observed a few hours after inoculation of the cornea, and until the third or fourth day there is a gradual increase in their number. They were found by v. Wasielewski in the experimental lesions produced by inoculation from the cornea of one animal to another carried through forty-six generations. Pfeiffer described, as before mentioned, a process of encapsulation followed by the formation of spore-like bodies, but both Pfeiffer and Guarnieri have subsequently declared that this appearance of segmentation is the

result of a degenerative process. Guarnieri has described a process of reproduction by the direct division of the intracellular body into two individuals, and claims to have actually observed this phenomenon in fresh material from variola and vaccine lesions studied upon a warm stage under the microscope. In hardened tissue appropriately stained dividing forms are rarely observed, although the number of inclusions increases very rapidly with the progress of the lesion, but occasionally the body is elongated or hour-glass in shape or consists of two separate parts. These appearances, according to Hückel, merely illustrate the great variety of forms which these bodies may assume.

The observations of Guarnieri, Monti, and others have shown that the intracellular bodies which have been described are constantly found in the pock of variola, in the neighborhood of the vaccine vesicle, and in the lesions in animals caused by inoculation with material from a vesicle of smallpox or vaccina. These observations, even though the parasitic character of the inclusions is denied, afford an additional argument in favor of the identity of smallpox and vaccina. Similar bodies do not occur in the normal skin or in diseased conditions other than those mentioned, though they resemble in some respects, as Gorini points out, cell inclusion of malignant tumors. Numerous efforts have been made to reproduce them by subjecting the cornea to various forms of irritation, but mechanical injury, burning, and various chemical irritants, including croton oil, osmic acid, and cantharides, fail to reproduce them, and inoculation with bacteria or purulent material from various sources has been equally unsuccessful.

Those who have studied the cell inclusions under consideration are not agreed as to their parasitic nature. The suggestion of Weigert and Babes that they are derived from the nucleus has received little support even from those who deny that they are parasitic microorganisms, since the stages in such a process of fragmentation have not been observed. As v. Wasielewski has pointed out, they are found in cells which appear otherwise normal and may occur in those of which the nucleus is undergoing karyokinetic division. Salmon thinks that they are leucocytes which have made their way into the epithelial cells and there undergone degenerative changes. Hückel dropped India ink into the eye of rabbits of which the cornea had been inoculated with vaccine lymph, but found no black granules in the specific cell inclusions, though they were present within a few readily recognized leucocytes which had made their way into epithelial cells. He found, moreover, that the nuclear body of the cell inclusion differs in its staining reactions from the nucleus of leucocytes. Hückel, after a most careful and painstaking study of vaccina corpuscles, concludes that they are formed from the protoplasm of the epithelial cell by the reaction

of some chemical substance produced by a hypothetical contagium of vaccina. Under this influence the protoplasm of the epithelial cell undergoes a local alteration, and a part of the altered material acquiring an affinity for nuclear dyes forms the nucleus-like structure within the cell inclusion. Hückel has not been able to trace the stages of this process, and he has not demonstrated the relationship of the intracellular bodies to structures occurring normally within the protoplasms, nor does he show their resemblance to any known form of degeneration.

The parasitic nature of the bodies under consideration can be proved only by the demonstration of vital phenomena. The amœboid bodies observed by Van der Loeff and Pfeiffer in the contents of vesicles of variola and vaccina have been thought to be identical with the bodies included within the cells. Guarnieri claims to have observed very slow amœboid movements of the intracellular bodies when the corneal epithelial cells containing them were examined upon a warm stage, and Monti and Pfeiffer claim to have confirmed his observation. Other observers, including Salmon, Hückel, and v. Wasielewski have not been able to observe such movement, and have emphasized the readiness with which errors of observation may occur.

Funck has recently described a method of multiplication which he believes can be observed in fresh vaccine lymph and in the contents of variola vesicles studied in hanging drop. In addition to the minute refractive slowly amœboid bodies observed by Van der Loeff and Pfeiffer, he finds, only in the uppermost part of the drop, large round or oval cysts, or sporoblasts, filled with very refractive bodies which he thinks are spores. Silvestrini and Podvyssotski, repeating the examinations of Funck, find only epithelial cells containing droplets giving the reaction of fat, and conclude that his bodies are merely fatty epithelial cells, probably from the sebaceous glands.

The parasitic nature of the peculiar intracellular bodies of vaccina and smallpox has recently been discussed at much length by v. Wasielewski, whose familiarity with protozoan parasites of man and of lower animals is well known. He reaches the conclusion that they are probably protozoa causing smallpox and the related disease of cattle and other animals, but bases his opinion altogether upon their morphological resemblance to protozoan forms and the absence of other demonstrable cause of the disease, of which the ready transmissibility indicates an infectious origin. Nevertheless the evidence of independent vital activity, as v. Wasielewski acknowledges, has not been furnished, and though another satisfactory explanation of their origin has not been demonstrated their parasitic nature is not proven.

LEUKÆMIA.

Protozoa-like bodies were first observed in leukæmic blood by Mannaberg in 1896. In fresh blood from a case of lymphatic leukæmia he found within the lymphocytes small bodies which stained with difficulty and exhibited amœboid movements, but since he was subsequently unable to find them in similar cases, he does not attribute to them an etiological significance. Löwit has recently described in both myelogenous and lymphatic leukæmia protozoa-like bodies demonstrable by special methods of staining in fixed specimens of blood, and has, he believes, been able to produce in animals a condition related to leukæmia and characterized by the presence of similar bodies in the blood. The nomenclature he has employed is somewhat confusing. To the parasite which he believes to be the cause of myelogenous leukæmia he has given the name Hæmamœba leukæmia, but subsequently finding a second smaller parasite in the blood of those suffering with lymphatic leukæmia he has called the first Hæmamœba leukæmia magna. To that which he found in lymphatic leukæmia he gave the designation Hæmamœba leukæmia vivax and later parva. He was unable to confirm his observations upon the last-named body, but subsequently discovered in cases of lymphatic leukæmia what he believed to be a parasite within the nucleus of the lymphocyte and to it gave the name Hæmamœba leukæmia parva intranuclearis. While to zoologists only binomial terms are acceptable as names of species the designation of Löwit may be provisionally used for convenience.

Hæmamœba Leukæmia Magna.—In order to demonstrate the bodies which he believes are characteristic of myelogenous leukæmia Löwit at first employed Loeffler's methylene blue applied with heat and partially decolorized with acid alcohol; he also used old solutions of thionin. These basic dyes stain both the specific bodies and the basophilic granules of the leucocytes, and only after prolonged investigation was Löwit able to devise a method of staining by which the bodies assume a characteristic appearance. In order to prevent distortion of the leucocytes a relatively thick film of blood is formed upon a cover slip by spreading a small drop with a platinum needle. The film after drying in the air is fixed by exposure to a temperature of 110° to 120° for from one to two hours. It is then stained for half an hour in a concentrated aqueous solution of thionin, and after washing with water and drying in the air is treated for from ten to twenty seconds with a solution of iodine in iodide of potassium and water (iodine 1 part, potassium iodide 2 parts, distilled water 300 parts). After

again washing and drying in the air the specimen is mounted in balsam. By this method the protozoa-like bodies assume a greenish color which varies from an olive tint to a blackish green. The nuclei of the leucocytes are stained pale brown; the products of nuclear degeneration and the basophilic granules vary in color from dark bluish-red to brown red. Later Löwit has recommended a variety of modifications of his specific stain.

Within the substance of the leucocytes, often merely applied to their surface, the staining methods just described demonstrate small bodies varying considerably in size and shape, the smallest being like granules, the largest a third, or even half, the diameter of the infected cell. More than one may be present in or upon a single leucocyte. Though they have a rounded outline, they are usually somewhat irregular in shape and are frequently provided with processes which suggest that they possess amœboid movements. Within the substance is often seen a structure which since it stains very deeply resembles a nucleus, but Löwit is not convinced as to its significance. The smallest rounded bodies frequently present a central clear area, and have in consequence a ring shape. This clear space in the larger forms has the appearance of a small cavity in which is occasionally recognized a minute nucleus-like body. Löwit has described the division of these amœboid bodies into a considerable number of granule-like segments, at times discrete, at times clumped together as a mulberry-like mass. These segments, he thinks, attack new leucocytes and thus propagate the infection. They represent an asexual process of multiplication.

Löwit also describes a second cycle of development by which are formed elongated spindle- or boat-shaped bodies frequently containing one or more nucleus-like particles. These occasionally occur outside the cells and apparently free in the plasma. They are not equally abundant in all cases of myelogenous leukæmia and may be wholly absent. They frequently possess, attached to their poles, one or two filamentous processes which are interpreted as flagella. Löwit suggests an analogy between these bodies and the crescents of æstivo-autumnal malaria, which are concerned in the sexual multiplication of the parasite outside the human body.

The bodies which have been described are found in or upon the leucocytes, never in the red corpuscles, and using the term employed by Danilewsky, Löwit regards them as leucocytozoa. Their number in different cases varies greatly, and it is particularly the small and large mononuclear leucocytes, the lymphocytes, that are affected. The myelocytes, the characteristic cells of myelogenous leukæmia, and the polynuclear leucocytes less frequently contain these bodies, and the eosinophile leucocytes are only rarely infected. The leuco-

cytes which are attacked show signs of degeneration, becoming swollen and vacuolated. The parasite, Löwit thinks, establishes itself in the blood, and by attacking and destroying the youngest leucocytes excites a very active compensatory proliferation; an excessive number of mononuclear neutrophilic cells or myelocytes are formed in the bone marrow and reach the general circulation. Great difficulty was encountered in demonstrating the specific bodies in the blood-forming organs, but in specimens hardened in alcohol and stained with Loeffler's methylene blue Löwit was able to convince himself that round or somewhat irregularly shaped bodies occur in the lymphocytes of the spleen and bone marrow, which by their staining reaction are identified with those in the peripheral circulation; he thinks they represent a resting stage of the parasite.

Löwit has attempted to support his conceptions by the experimental inoculation of animals. Numerous fruitless attempts have been made by Mosler, Nette, Teichmüller, and others to transfer leukæmia to animals, but Löwit claims to have produced in rabbits, by the intravenous inoculation of material from leukæmic organs, a condition usually fatal, which though it differs from the human disease is closely related to it. Though, as Löwit states, the condition cannot be designated leukæmia of rabbits, it may be regarded as a leukæmic infection. The blood of infected animals shows a variable increase of mononuclear leucocytes, often constituting seventy to eighty per cent. of the total number of colorless corpuscles, while the bone marrow gives evidence of active cell proliferation, and in the spleen there is active destruction of red corpuscles. The body weight diminishes and death occurs with diarrhœa. In the blood, and in the blood-forming organs, Löwit was able to demonstrate the specific bodies of myelogenous leukæmia.

The observations of Löwit have attracted much attention and have received by no means universal acceptance. Vettodini has identified Löwit's hæmamœba in three cases of myelogenous leukæmia, but in a variety of other diseases was unable to discover it. Löb found the specific bodies in two cases of myelogenous leukæmia, but is undecided as to their significance. A considerable number of observers, Türk, Kraus, Litten, and Michaelis, after repeating the investigations of Löwit, do not regard as parasites the bodies he describes, but think they are artificial products of his staining methods. Pinkus points out that Hæmamœba magna is found in that variety of leucocyte which is least characteristic of myelogenous leukæmia, and states that he has found similar bodies in the lymphocytes in a case of lymphatic leukæmia. The most important opposition to Löwit's views has come from Türk, who claims that the bodies described by Löwit are not protozoa, but artificial products caused by the action of basic stains

in a watery solution upon the basophilic granules of the mast cells. In the blood of normal rabbits which contains mast cells in considerable numbers he claims to have demonstrated by Löwit's specific stain bodies which are identical with Löwit's hæmamœbæ, and states that the number of infected corpuscles corresponds to the number of mast cells demonstrable by other methods. These facts explain, he thinks, the inoculation experiments of Löwit, and with repeated attempts he was unable to reproduce in rabbits the condition which Löwit described. On the other hand Löwit was unable to identify his bodies in the specimens exhibited by Türk before the Congress for Internal Medicine, held at Wiesbaden in 1900.

The parasitic character of the bodies described by Löwit has not been proven, and they do not appear to present charateristics analogous to those of the malarial parasites or other protozoa with which we are familiar. Since they are observable with great difficulty, if at all, in fresh specimens of blood or of tissues, the demonstration of independent vital phenomena is obviously great. The facts brought forward by the opponents of Löwit strongly suggest that his specific bodies are artificial products, but they have afforded no convincing explanation of their origin.

Hæmamœba Leukæmia Parva Intranuclearis.—Less worthy of detailed consideration are the bodies which Löwit has described as protozoan parasites in cases of lymphatic leukæmia. By the use of Loeffler's methylene blue, followed by decolorization with acid alcohol, one of the methods employed to demonstrate his Hæmamœba magna, Löwit found in the hæmatopoetic organs and occasionally in the peripheral blood from cases of lymphatic leukæmia metachromatic bodies within the nuclei of the lymphocytes, and gave to them the name Hæmamœba leukæmia parva (vivax). Subsequent observations lead him to conclude that these bodies, which occur in leucocytes showing other evidences of degeneration, were the products of nuclear degeneration. By a wholly different method of staining he has found in cases of lymphatic leukæmia within the nucleus of the lymphocytes other bodies, the structure of which, he thinks, identifies them as protozoa. Löwit used the polychrome methylene blue employed by Nocht in his modification of Romanowsky's stain for the malarial parasites. It is applied with heat and after decolorization with a weak watery solution of hydrochloric acid, minute bodies, a sixth to a half the diameter of a red blood corpuscle, round, oval, or boat-shaped, retain a reddish-violet color. A vacuole-like area often gives a ring-shaped outline, while within is occasionally a dark granule. In some instances the presence of two or four clear areas, and an indentation of the outline of the body, suggest division. Some uncertainty attends the staining reaction which Löwit describes; it is only in prop-

erly decolorized specimens that these bodies are demonstrable, and their demonstration can be effected only by practice. By a slight modification of the method Löwit is able to identify the bodies in hardened tissue from the blood-forming organs, not only in cases of leukæmia but with pseudoleukæmia as well.

Türk has again attacked the views of Löwit and declares the intranuclear particles to be constituents of the normal nucleus, but demonstrable only after the lymphocyte has been subjected to injurious artificial conditions, as the result of which it stains palely and becomes vacuolated. In the blood of three chlorotic patients Türk was able to demonstrate Löwit's intranuclear bodies in specimens prepared after crushing the leucocytes by careful compression of the fresh blood between two cover slips. He thinks that these bodies are readily demonstrable in leukæmia because the lymphocytes are less resistant to injury than in the normal blood.

YELLOW FEVER.

BY

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YELLOW fever is a specific infectious disease characterized by a single febrile paroxysm of from two to five days' duration, by the presence of albumin in the urine, an icteric color of the skin, and a tendency to passive hemorrhages from mucous surfaces—especially from the stomach, producing "black vomit." The specific infectious agent has not been discovered, but it has been demonstrated that it is present in the blood during the first two or three days of the attack, and that the disease is transmitted from man to man by an intermediate host—a mosquito of the genus Stegomyia.

Yellow fever has a comparatively restricted *geographical range*. Occasional epidemics have occurred in North America in every one of our seaport cities as far north as Boston and in the Mississippi valley as far north as St. Louis, but it has never established itself as an endemic disease within the limits of the United States. The cities of Havana, Rio de Janeiro, and Vera Cruz have been endemic foci of the disease for many years and it has prevailed as an epidemic at all of the principal seaports of the Gulf and Atlantic coasts of South America as well as in the West Indian Islands; also upon the Pacific coast of Mexico and South America. Its prevalence in Africa has been limited to the west coast and in Europe to the Iberian peninsula. It is unknown elsewhere in Europe or in Asia.

The idea that yellow fever may originate *de novo*, as a result of certain conditions relating to climate, decomposition of organic matter, etc., was entertained by many physicians during the early part of the last century, but there is no longer any doubt that it is a specific infectious disease which cannot originate independently of a previous case. As in the case of other infectious diseases its origin is involved in obscurity and can only be a matter of speculation. The early historians, Herréra, Oviédo, Rochefort, and others, make reference to epidemics among the natives which occurred prior to the discovery of the Antilles, and to fatal pestilential diseases among the first settlers of these

islands; but their accounts are not sufficiently exact to enable us to affirm that the disease referred to by them was yellow fever. The west coast of Africa was discovered and colonized to some extent before the discovery of America, but the first authentic accounts of the prevalence of yellow fever on this coast date back only to the year 1778, over two centuries after the first settlements had been established. On the other hand, this very epidemic of 1778 at St. Louis (Senegal) was traced to importation from Sierra Leone, a portion of the African coast which, according to Hirsch, "appears to be the headquarters of the disease, and the starting-point of its epidemic inroad into the territories lying to the north and south, as well as into the West African islands."

History.

I cannot attempt to give a history of the prevalence of yellow fever in the West Indies, in Mexico, or in South American countries, but, in view of its proximity to the United States and commercial importance, will give some account of the sanitary history of Havana in so far as it relates to this disease.

The historian Pezuela records the prevalence of a malignant pestilential disease in Havana in 1648, a year in which, as we have seen, yellow fever was epidemic in the islands of Guadeloupe and Barbadoes. He says: "In this year there occurred in Havana a great pest of putrid fevers which remained in the port almost all the summer. A large part of the garrison and a larger part of the crew and passengers in the vessels died." The epidemic continued the following year, and in 1653–54, according to the author above quoted, "the epidemic was renewed with equal fury"; and in 1655 "in the capital continued to carry away its victims without regard to rivalries and passions." According to Dr. S. E. Chaillé, president of the Havana Yellow-Fever Commission (1879), from whose report we have quoted the above extracts from Pezuela, there is no historical evidence of the prevalence of yellow fever in Havana for more than a hundred years after the date mentioned. "On the contrary, there are repeated records of the great salubrity of the climate and the absence of epidemic diseases."

It was not until the year 1761 that yellow fever established itself in the previously healthy city. Pezuela gives the following account of its introduction: "Although Havana is situated on the northern boundary of the torrid zone, it was very justly considered one of the most healthy localities on the island before its invasion, in a permanent manner, by the *vomito negro*, imported from Vera Cruz in the summer of 1761. In May there came from Vera Cruz, with materials and some prisoners destined for the works on the exterior fortifications of Havana, the men-of-war *Reina* and *America*, which communicated to the neigh-

borhood the epidemic known by the name of 'vomito negro.' At the end of the following June there were stationed in this port nine men-of-war, despatched from Cadiz, and sent to the chief of the squadron, Don Entienne de Hevia; they brought a reinforcement of 2,000 men. More than 3,000 persons succumbed to the epidemic on this, *the first appearance* of the vomito."

From this time to the termination of Spanish rule in the island the new levies of troops sent from Spain to Cuba continued to suffer enormous losses from the endemic pestilence. In 1779 there arrived from Spain, then at war with Great Britain, "an army of 3,500 men, which was immediately decimated by the vomito." In 1780, during the month of August, an army of 8,000 men was landed in Havana, which during the two following months suffered a loss of about 2,000 men with the vomito. Pezuela records the fact that in 1794, in the garrison and squadron, there were more than 1,600 victims to the disease.

The endemicity of yellow fever in Havana was fully established by the researches of the commission sent to that city in 1879, by the national board of health. Dr. Chaillé, president of this commission, says in his elaborate report, published in 1881: "Since 1761 yellow fever has prevailed certainly in Havana, and probably in other places in Cuba, every year, and the dates of prevalence recorded in our text-books indicate no more than the years of greatest prevalence. The disease prevails in Havana, and in some other places in Cuba, not only every year, but also every month in the year; records in 1837 indicate that at that date the monthly prevalence had become habitual in Havana; the statistics, solely of the military and civil hospitals, prove that during the 408 months, 1856–79, there was only one single month free from an officially recorded case of yellow fever."

The following tables are from the "Preliminary Report of the Havana Yellow-fever Commission":

MONTHLY MAXIMUM AND MINIMUM DEATHS BY YELLOW FEVER IN HAVANA DURING THE TEN YEARS 1870-79.

Months.	Minimum.	Maximum.	Months.	Minimum.	Maximum.
January	6	32	July	68	675
February	4	24	August	70	416
March	4	32	September	35	234
April	4	37	October	28	185
May	13	103	November	5	150
June	66	378	December	9	82

In no one of the ten years 1870-79 were there ever fewer deaths than in the first, no more than in the second, column, and the total deaths by yellow fever for each year were as follows:

TOTAL DEATHS BY YELLOW FEVER IN HAVANA.

In 1870	665	In 1875	1,001
In 1871	991	In 1876	1,619
In 1872	515	In 1877	1,374
In 1873	1,244	In 1878	1,559
In 1874	1,425	In 1879, to October 1st	1,353

I have not at hand statistics covering the years 1880 to 1895, but the number of deaths has diminished in a notable manner since the American occupation of Cuba. In his report as chief sanitary officer, for the month of October, 1901, Major Gorgas, Surgeon U. S. A., says:

"The most prominent feature of the statistics this month is the fact that there have been no deaths from yellow fever in the city, and not a single case. It will be seen in the body of the report that three cases are reported, but these three cases were taken sick in September and carried forward into October.

"It will be seen that October, on the average, in the past ten years, has been one of the severest months for yellow fever. The maximum number of deaths from yellow fever since 1889, for this month, occurred in 1896 when we had 240 deaths; the minimum, in 1899, when we had 25 deaths; the average, 66.27 deaths; this year, no deaths and no cases. Last year, 1900, we had for October, 308 cases and 74 deaths.

"The fact that the marked improvement is not confined to October, but has taken place each month since we have been devoting ourselves to the mosquito, is particularly emphasized by considering the yellow-fever year beginning the first of April.

"Since 1889, for these months, we have had on the average, 362.16 deaths; the maximum, in 1896, 871; the minimum, in 1899, with 61; this year, 0.

"The change cannot be due to improvement in general hygiene, from the fact that last year, for this month, we had 74 deaths; this year, none. While there has been improvement in the general hygienic conditions, there could not have been so vast a difference as this would represent. The improvement in general hygiene is measured best by the general death rate. The death rate for October, 1900, was 24.33; this year, 1901, 20.17."

The explanation of this remarkable reduction in the mortality from yellow fever will appear later, when the subjects of etiology and prophylaxis are discussed.

In the United States numerous epidemics have occurred at all of our seaport cities upon the Gulf of Mexico and the South Atlantic seaboard, and especially in the cities of New Orleans, Mobile, and Charleston. From 1817 to 1858 the disease prevailed in the city of

New Orleans to a greater or less extent nearly every year and was generally believed by residents of that city to be endemic. The mortality from the disease for a period of twenty-four years is shown in the following table:

1847	2,259	1859	....
1848	850	1860	....
1849	787	1861	....
1850	102	1862	....
1851	16	1863	....
1852	415	1864	....
1853	7,970	1865	....
1854	2,423	1866	....
1855	2,670	1867	3,093
1856	74	1868	....
1857	199	1869	....
1858	3,889	1870	587

This table shows annual prevalence during the twelve years prior to 1859 and absence of the disease for seven years subsequent to this date, when the great epidemic of 1867 occurred, without doubt as a result of importation.

Great Epidemics in the United States. 1793.—The city of Philadelphia, after enjoying an immunity from yellow fever for thirty-one years, suffered in 1793 a devastating epidemic. This epidemic, no doubt, resulted from importation, although a clear history of its introduction was not made out at the time, and the leading physicians of the city were inclined to attribute it to local origin, as a result of unsanitary conditions in connection with an unusually high temperature. La Roche says: "Dr. Rush and others laid great stress on a quantity of damaged coffee which was exposed, during the latter part of July, in a place (on a wharf and in the adjoining dock) and under circumstances which favored decomposition. Its smell was highly putrid and offensive, insomuch that the inhabitants of the houses in Water and Front streets, who were near to it, were obliged in the hottest weather to exclude it by shutting the doors and windows. Even persons who only walked along those streets complained of intolerable fetor, which, upon inquiry, was constantly traced to the putrid coffee."

As usual, the early cases were not recognized as yellow fever. Dr. Rush says: "The report of a malignant and fatal fever being in town spread in every direction, but it did not gain universal credit. Some of those physicians who had not seen patients in it denied that any such fever existed, and asserted (though its mortality was not denied) that it was nothing but the common annual remittent of the city. Many of the physicians joined the citizens in endeavoring to discredit the account I had given of this fever, and, for a while, it was treated

with ridicule or contempt. Indignation in some instances was exerted against me." History repeated itself in this particular many times in subsequent epidemics. The early cases, even in cities like New Orleans where the physicians are well acquainted with the disease, are frequently called by some other names—"bilious fever," "pernicious fever," "malarial fever," etc.—and the physician who first ventures to name the prevailing disease "yellow fever" is treated with ridicule or with indignation.

It was not until the middle of August that a rapid succession of fatal cases convinced the physicians of the city that the fatal West Indian pestilence was again present in Philadelphia.

The presence of the disease was officially recognized on the 22d of August, when the mayor of the city gave orders for the cleaning of streets and general purification of the city. The disease continued to extend until early in October, when it reached its height. It did not cease entirely until about the 8th of November. During this short season of prevalence it caused an enormous mortality, distributed as follows: "August, 325; September, 1,442; October, 1,976; November, 118" (La Roche).

The population of the city at this time is estimated to have been a little more than 40,000, which gives a mortality of ten per cent. of the total population (total mortality 4,040). As more than 12,000 of the inhabitants fled from the city, the proportion of those who were attacked was very great. La Roche estimates the total number of cases at 11,000.

1797.—The epidemic of this year in the city of Philadelphia was less extended and less fatal. The whole number of deaths is estimated to have been about 1,300. The disease, as usual, commenced in the vicinity of the wharves (about the end of July). Unsanitary conditions, described by physicians who were witnesses of the epidemic, were supposed to furnish the favorable local nidus for the exotic germ, which, according to a report of the College of Physicians of Philadelphia made in response to a request from the governor, was imported by two vessels, one from Havana and the other from Port au Prince. In this report the College of Physicians, contrary to the prevailing popular opinion, and that of many prominent physicians, took the ground that the unsanitary local conditions were simply secondary or accessory causes, and recommended "a more stringent system of quarantine regulations as the most effectual means of preventing the recurrence of the disease" (La Roche).

1798.—The epidemic of 1797 was followed the next year by a still greater one, which was not confined to the city of Philadelphia alone. The disease prevailed also in Boston (mortality 200), in Portsmouth, N. H. (mortality 100), in Newport, R. I. (mortality 2), in New Lon-

don, Conn. (mortality 81), in New York (mortality 2,080), in Wilmington, Del. (mortality 250), and in Charleston, S. C. The mortality in Philadelphia was 3,645, distributed as follows: August, 626; September, 2,004; October, 943; November (from the 1st to the 5th), 72. The mortality, in proportion to the number of cases, in the city of Philadelphia, was enormous, being, according to La Roche, about as 1 to 1.27 of those attacked, or nearly eighty per cent. This is accounted for partly by the fact that the better classes of the community left the city as soon as possible after the outbreak of the disease, and the cases which occurred were consequently among the poorer classes, who inhabited the worst portions of the city. The prevailing ideas as to the treatment of fevers by depleting measures, were doubtless responsible to some extent for the excessive mortality. "The College of Physicians, faithful to the theory so long entertained by it in relation to the cause of the disease, assigned to the epidemic this year, as it had done to those of preceding seasons, a foreign origin" (La Roche).

1802.—An epidemic of smaller proportions prevailed in the year 1802, causing a mortality in Boston of 60, in Philadelphia of 307, in Wilmington of 86, in Charleston of 96. The disease also prevailed "extensively" in Baltimore, but no record of mortality is given. The prevalence of the disease at the seaports mentioned, especially before the time of railroad communication, is not to be ascribed to an extension from one to the others, or to "an epidemic constitution of the atmosphere"; but it doubtless occurred, for the most part, as a result of independent importation from the usual source of the disease—the West Indies. Thus we find that in 1802, while Boston and Philadelphia suffered epidemics, New York, lying between the two infected points, was free from the disease (two cases only are reported).

1853.—Passing over the minor epidemics, for the most part limited to a single city, or by coincidence merely to two or more distant seaports, we come to the epidemic of 1853, which extended through portions of the States of Florida, Alabama, Louisiana, Mississippi, Arkansas, and Texas. The towns which suffered in *Florida* were Pensacola, Milton, and Tampa. In *Alabama*, Mobile (mortality 115), Cahawba, Citronelle, Demopolis, Fulton, Hollywood, Montgomery (mortality 35), Selma (mortality 32), were the principal towns visited by the scourge. In *Louisiana* the disease prevailed at New Orleans, with a mortality of 7,970, at Alexandria, Algiers, Bay St. Louis, Bayou Sara, Centreville, Clinton, Coultierville, Franklin, Opelousas, Pattersonville, Plaquemine, Shreveport, Thibodeaux, Trenton, Washington, and various smaller places. In *Mississippi* Biloxi, Brandon, Clinton, Grand Gulf, Greenwood, Jackson, Natchez, Pascagoula, Pass Christian, Port Gibson, Washington, Woodville, Yazoo. In *Arkansas*, Col-

umbia, Grand Lake, Napoleon. In *Texas*, Brownsville, Cypress City, Galveston, Hockley, Houston, Indianola, Liverpool, Richmond, Saluria.

1867.—The epidemic of this year was widely extended in the State of Texas. The first recognized case in New Orleans occurred on the 10th of June. The total mortality in this city was 3,093. Other towns visited in *Louisiana* were New Iberia and Opelousas. In *Texas* the first cases occurred at Galveston on the 26th of June, and the total mortality in this city was 1,150. Other places visited by the epidemic were Alleyton, Anderson, Austin, Bastrop, Brenham, Calvert (mortality 250), Chapel Hill (mortality 123), Corpus Christi, Danville, Goliad, Hempstead (mortality 151), Huntsville (mortality 130), Independence, Indianola (mortality 80), La Grange (mortality 200), Liberty, Millican, Navazota (mortality 154), Oldtown, Port Lavacca, Rio Grande City (mortality 150), Victoria (mortality 200).

1873.—Florida, Alabama, Mississippi, Louisiana, and Texas again suffered from an epidemic of yellow fever in the year 1873. At Pensacola, Fla., the first recorded case occurred August 6th, and the total mortality was 61. In *Alabama* the disease appeared at Mobile on the 21st of August, and the total mortality was but 27; Montgomery suffered a loss of 102. In *Louisiana* the mortality in the city of New Orleans was only 225, although the epidemic had its origin in this city. It was imported by the Spanish bark *Valparaiso*, which sailed from Havana June 15th in ballast, arrived at the New Orleans quarantine station June 24th, was detained two days and came to the city June 26th. The first case was in the mate of this vessel, who was taken sick on board July 4th, while she was lying at the wharf. But for the sickness and death of the mate of the *Valparaiso* the origin of this epidemic would have remained obscure, and the believers in the local origin of the disease would have had a strong case, for no other cases of the disease occurred on the *Valparaiso*. This is explained by the fact that the crew consisted of acclimated Spaniards, and the mate seems to have been the only susceptible person on board who could serve as a test of the infection of the vessel at her port of departure. From New Orleans the disease was carried to Memphis by the river steamer *Bee*. It caused a mortality in this city of 2,000. River steamers from New Orleans also carried the disease to Shreveport, La., where the mortality was 759. From Shreveport a refugee fled to the town of Calvert, Texas, where he was taken sick and died; an epidemic followed with a total mortality of 125. The disease was also introduced by refugees into the town of Marshall, Texas, where 36 deaths occurred. The epidemic of this year at Pensacola, Fla., was due to an independent importation, by the ship *Golden Dream*, and Montgomery, Ala., became infected through refugees from Pensacola.

1878.—The last great epidemic of yellow fever in the United States was that of 1878, which invaded 132 towns, and caused a mortality of 15,934, out of a total number of cases exceeding 74,000. The origin of this epidemic was traced by the president of the Louisiana State Board of Health (Chopin) to the steamer *Emily B. Souder*, which arrived from Havana May 23d, and was moored at the foot of Calliope Street, New Orleans. Dr. Chopin says: "The first cases of yellow fever in New Orleans in 1878 were, undoubtedly, two of the officers of the above steamship, namely, Clarke, the purser, and Elliott, one of the engineers." Infected centres were developed in the vicinity of the houses in which these men were sick, but not until after an interval of several weeks.

Etiology.

It is a well-established fact that yellow fever prevails more frequently in seaports than in inland towns, and that, when epidemics prevail in the interior, their origin can commonly be traced to the nearest seaport, or to intermediate towns in communication with it. Towns upon or near the coast which have no commerce are no more subject to invasion by yellow fever than are interior towns, unless it be by reason of their proximity to a seaport. Moreover, the frequency of epidemics in our Southern seaports, before the era of efficient quarantine administration, bears a direct ratio to their commercial importance, and especially to their commercial intercourse with Havana or other endemic foci of the disease. Thus New Orleans suffered epidemics of greater or less magnitude in 48 out of the first 60 years of the present century. During the same period (1800–1860) Charleston suffered 28 epidemics, Mobile 22, Pensacola 17, Savannah 9, Galveston 7. That local conditions are favorable for the development of an epidemic at many of our interior towns, especially those located on great rivers, near the sea level, in the Southern States, is amply proved by the epidemic of 1878. That yellow fever does not occur at these towns, except as a result of importation, is beyond question. So, too, in seaport cities there is no reason for believing that any radical change has occurred in local conditions during the past twenty-eight years; yet during this time New Orleans has suffered only six epidemics, while during a corresponding period (twenty-eight years) prior to 1860 there were twenty-two years of epidemic prevalence of the disease. A similar comparison for Charleston shows fourteen years of epidemic prevalence prior to 1860, and only one since.

Up to the year 1860 there were many advocates of the *local origin* of the disease in these seaports, and the disease was considered endemic by many physicians, both in Charleston and in New Orleans. But to-day scarcely any one questions the fact that the disease, notwith-

standing its frequent prevalence, was due to importation, and that it is nowhere endemic within the boundaries of the United States. It is not improbable, however, that in certain instances the "germs" of the disease have survived the winter season, and that sporadic cases and epidemics have occurred as a result of importation, dating back one or more years. It is claimed that the epidemic of 1879, in the city of Memphis, was not due to a new importation, but resulted from the hibernation of germs (mosquitos ?) in houses infected in 1878. Dr. Thornton, president of the Memphis Board of Health during these epidemics, says: "The disease appeared in houses in the suburbs, which were infected last year"; and states further that the first case reported to the Health Office occurred on the 8th of July, at which date the disease was not prevailing in any part of the United States. In New Orleans, in epidemic years, cases have sometimes continued to occur during the greater part of the month of December, and in Tampa and Plant City, Fla., where yellow fever was epidemic in the summer of 1887, cases are said to have occurred at intervals throughout the winter. Admitting, then, the probability that the recurrence of the disease in our Southern seaports has sometimes been due to the preservation of the infectious agent in an active state throughout the winter, we must insist, nevertheless, that there is no satisfactory evidence of the *de novo* origin of the disease from local causes, either in our own country or elsewhere; and that, wherever its original habitat may have been, the prevalence of the disease within the period to which our authentic historical records relate has been due to the importation of cases, or of infected mosquitos, from a previously infected place. In other words, the disease is due to a specific infectious agent.

After the great epidemic of 1878 a board of experts was appointed by authority of Congress, to make investigations with reference to the origin and spread of the disease. One of the conclusions arrived at by this board is stated as follows: "The most frequent agency in the dissemination of yellow fever from place to place is found in yellow-fever patients; and more epidemics of yellow fever have resulted from the introduction into previously exempt places of persons sick of the disease, or falling sick after arrival, than from all other causes. To what extent the body of the sick person is responsible for this result, and to what extent his clothing and baggage are responsible for it, is not known."

While the origin of epidemics in the United States can as a rule be traced directly to the arrival of a ship from an infected port, and usually to an imported case of the disease, it has occasionally happened that the disease has developed apparently as a result of the arrival of a ship from an infected port, when no case of the disease has occurred on board or among its passengers after arrival. This has led to the

inference that the specific infectious agent might be imported, independently of the sick, in infected articles of clothing or merchandise or in ballast taken from an infected locality. This inference has furnished the basis of the measures of prophylaxis commonly employed at our seaport cities, an essential feature of which has been the "disinfection" of baggage, of the ship, and of certain kinds of merchandise. In view of the recent discovery that yellow fever is transmitted from man to man by mosquitos of the genus Stegomyia we can now readily account for the occurrence of the disease under the circumstances mentioned without supposing that the germ was introduced in fomites of any kind. Infected mosquitos from the port of departure, coming as "stowaway" passengers in the hold of the ship, could readily transmit the disease to those engaged in unloading the vessel or to those living in the immediate vicinity of the dock at which she was lying. No doubt this is the true explanation of the origin of epidemics which have been ascribed to the unloading of ballast, to infected freight or baggage, to the floating ashore of mattresses, etc.

That yellow fever is not directly transmitted from the sick to susceptible individuals, by personal contact, has long been maintained by the present writer and by many physicians who have had opportunities for studying the origin of epidemics.

Formerly the battle between the contagionists and the non-contagionists was one involving the question of local origin on one side, together with a strenuous denial of the transmissibility of the disease and the value of quarantine restrictions. The contagionists, on the other hand, insisted upon the exotic origin of the disease and its transmissibility by ships and persons. And to this extent they were right.

It is well known to the people of the City of Mexico that a visit to the seacoast city of Vera Cruz during the epidemic season is likely to result in an attack of yellow fever. It is also well established that those who fall sick with the disease after their return to the City of Mexico never communicate it to others who are closely associated with them as attendants, etc. The same is true at the health resort Petropolis, located in the mountains within a few hours' ride of the city of Rio Janeiro. Frequently individuals fall sick in Petropolis who have visited the infected city of Rio. Never do they communicate the disease to others. This is also the experience of the physicians in charge of hospitals, *e.g.*, the Charity Hospital of New Orleans; so long as the hospital and its vicinity remain uninfected cases do not originate in the hospital, although yellow-fever patients may be admitted to the wards with non-immune persons suffering with other diseases, and be cared for by susceptible attendants.

In his report upon the camps established near Memphis in the epidemics of 1878 and 1879, Colonel Cameron makes the following state-

ment: "It was found necessary that the officer in authority should set an example of constant indifference to attack in order to appease, as far as possible, the constant anxiety of the population under his charge. Especially was this true in 1878, as depopulation went on slowly that year, and infected people poured daily into the camps from the more pestilential portions of the city. Very many reached camp with the fever in them, so that as many as seventeen persons fell victims in one night, not a few in their tents. *In no instance, however, did they communicate the disease to their families or bed-fellows,* so far as could be traced."

In the same epidemic (1878) Dr. Minor reports that over thirty cases were discovered among refugees in Cincinnati, O., and says: "No physician or nurse contracted the disease, and in no instance did it exhibit any tendency to spread." The same was true in Nashville the same year; twenty imported cases occurred in different parts of the city without any local cases resulting from them (report of Nashville Board of Health). Evidence of this kind could be extended to fill a volume, but sufficient has been presented to establish the statement made, and the reader may be referred to the "Proofs of Non-Contagion" in the second volume of the classical work of La Roche (pp. 236–566).

There is no satisfactory evidence that the disease is ever contracted by the use of contaminated food or water, as is the case with typhoid fever or cholera, but it is frequently contracted by persons who visit an infected locality and who have not come in direct contact with any person sick with the disease. It has also been a popular belief that visits to such a locality at night are more dangerous than during the day. In the light of our present knowledge this is readily understood. Yellow fever and the malarial fevers are more frequently contracted "by exposure to the night air" because mosquitos are more active in the evening and after sundown. The board of experts appointed to investigate the epidemic of 1878 adopted, among others, the following conclusions:

"(6) Yellow fever is a disease of singular local attachments. It often becomes epidemic in one section of a city, and sometimes a very small section of it, while it fails to present itself at all in other sections of the same city, and in these localizations it exhibits a remarkable indifference to topographical and social surroundings.

"(7) In the dissemination of yellow fever, atmospheric air is the usual medium through which the infection is received into the human system."

These conclusions are in accord with our present knowledge as to the mode of transmission. "Atmospheric air is the usual medium through which the infection is received into the human system," but

it is by infected mosquitos carried through the air by currents of wind or by their own independent powers of flight that the germ is introduced into the human system.

The discovery that yellow fever is transmitted from man to man by the mosquito affords a rational explanation of all the observed facts relating to the influence of altitude and climatic conditions upon the prevalence of the disease. Yellow fever is limited as regards its prevalence to localities where the intermediate host of its specific germ is to be found and to seasons during which this intermediate host is active. In localities where mosquitos of the genus Stegomyia are able to survive the winter months the disease may establish itself as an endemic, either by the occurrence of a succession of cases resulting from the transmission of the germ by active mosquitos, or by the hibernation of infected mosquitos. We already have experimental evidence that infected mosquitos may survive and transmit the disease for a period of fifty-seven days.

In a recent paper (October 26th, 1901) by Reed and Carroll on "The Prevention of Yellow Fever," they say: "After the mosquito has once become dangerous, how long it remains capable of conveying the disease, although important, has not been determined. We have reported cases of yellow fever caused by the bites of Stegomyia at intervals varying from twelve to fifty-seven days after contamination. Here the dangerous interval was forty-five days, but as one of these insects lived until the seventy-first day after biting a yellow-fever patient, the dangerous interval would here be prolonged to fifty-nine days, or a little over eight weeks. In our experience, the infected insect appears to live about as long as the non-infected mosquito, so that the answer to this question would depend upon the length of life of the mosquito. This we do not know. While in captivity the majority of mosquitos do not survive, with the best of care, more than about five weeks, and many die within half of this time; we are ignorant as to the length of time during which they may live when under natural conditions. Certainly, during summer weather this will depend largely on the opportunity which the moquito has of obtaining access to water."

In the writer's paper on yellow fever in the first edition of the "Reference Handbook of the Medical Sciences" (Vol. VIII.) published in 1889, the following remarks are made with reference to the influence of altitude and climatic conditions upon the prevalence of the disease under consideration:

"*Altitude.* The facts do not justify the conclusion that the limitations as to altitude depend solely upon the lower temperature of elevated regions. As pointed out by Hirsch, the disease stops short at many points in the West Indies where the climate is still in the high-

est degree tropical. On the other hand, there have been epidemics in cool weather at very considerable altitudes, as, for example, at Newcastle, in Jamaica (elevation about 4,000 feet). In the Antilles the disease has rarely appeared at a height of more than 700 feet. In Mexico it has prevailed at Cordova (2,500 feet), but is unknown in the cities of Orizaba, Jalapa, and Puebla, which have an elevation of more than 3,000 feet. In Spain a single limited outbreak has occurred at Madrid, which is about 2,000 feet above the sea level; but with this exception the altitudinal range has rarely exceeded 1,000 feet. In the United States the most elevated locality in which the disease has prevailed as an epidemic is Chattanooga, Tenn., which is 745 feet above the sea level. Yellow fever is essentially a disease of the *seacoast*, and while in great epidemics it may become widely diffused in the interior, it follows, for the most part, the course of *navigable rivers*. It is a disease of *cities* and towns of considerable size, and rarely extends to small country villages, or among the scattered rural population. In seaport towns it frequently makes its first appearance in the *vicinity of the wharves*, or in localities frequented by sailors. . . . Conditions relating to *soil and geological formation* have not been shown to influence in an essential manner the development or diffusion of the disease. On the other hand, the numerous epidemics which have occurred on shipboard show that the disease is quite independent of such conditions. . . . *Meteorological conditions* control in a most decided manner the prevalence of the disease in localities where it is endemic, and its epidemic extension when new infected centres are established among a susceptible population. The influence of *temperature* is shown by the fact that it is a disease of the tropics and of hot seasons; that it prevails throughout the year in the cities of Rio Janeiro, Havana, and Vera Cruz, although to a much less extent during the cool season; while in more temperate regions its prevalence is limited to the summer season. It does not prevail as an endemic disease in places which have a mean winter temperature much below 65°, and as a rule epidemics are not developed at a lower temperature than 75° to 80° F. The approach of cool weather checks the progress of an epidemic, and it is arrested completely when the temperature falls to the freezing point. There are, however, numerous facts which indicate that the infectious agent is not destroyed by a freezing temperature, although rendered inactive. Epidemics which have been checked by frost have been revived by the recurrence of warm weather, and in certain instances in temperate regions the germ has survived the winter, and a second epidemic has occurred without a new importation (Memphis, 1878–79; Cadiz, 1800–01; Malaga, 1808–09). Epidemics which originate early in the season often terminate before there is frost, simply because the susceptible material is exhausted; but

when strangers venture within the infected area they furnish evidence of the continued activity of the morbific poison, by falling victims to the disease. The influence of *season* is shown by the following tables:

MORTALITY FROM YELLOW FEVER IN RIO JANEIRO DURING THE YEAR 1886.

Month.	Total deaths.	Mean temperature.	Total rainfall.
January	135	77.5°	1.03
February	234	76.3	10.94
March	347	77.5	3.02
April	220	75.0	8.81
May	48	69.2	.35
June	18	67.3	1.68
July	9	65.5	1.55
August	2	65.5	5.37
September	0	68.5	4.59
October	1	69.2	1.37
November	0	72.9	1.37
December	1	74.1	8.92
Total	1,015	....	49.00

MORTALITY FROM YELLOW FEVER IN RIO JANEIRO FROM JANUARY, 1851, TO JULY, 1870. (HIRSCH.)

Epidemic season.		Non-epidemic season.	
January	1,118	July	243
February	1,760	August	164
March	1,782	September	108
April	1,434	October	104
May	996	November	116
June	557	December	223
Total	7,597 = 89 per cent.	Total	957 = 11 per cent.

MORTALITY FROM YELLOW FEVER IN THE CITY OF HAVANA FOR TEN YEARS—1870–1879, INCLUSIVE—(CHAILLÉ, REPORT TO NATIONAL BOARD OF HEALTH.)

Month.	1870.	1871.	1872.	1873.	1874.	1875.	1876.	1877.	1878.	1879.	Average of ten years.
January	6	18	20	32	7	16	24	8	23	11	17
February	4	23	13	23	4	16	24	9	13	13	14
March	4	12	4	27	18	32	29	11	5	6	15
April	6	54	4	37	22	34	33	8	28	13	24
May	14	91	13	127	85	32	103	16	53	40	57
June	66	201	68	378	172	142	292	143	184	237	188
July	112	234	68	416	361	187	675	249	504	475	328
August	201	138	70	127	416	144	250	285	374	417	242
September	91	72	59	35	186	102	97	234	179	148	120
October	77	55	38	28	91	109	42	185	106	44	78
November	49	51	85	5	42	105	31	150	53	31	60
December	35	42	73	9	21	82	19	76	34	9	40
Total	665	991	515	1,244	1,425	1,001	1,619	1,874	1,559	1,444	....

"The above tables show us that temperature is only one of several factors which control the prevalence of the disease, for with a tolerably

uniform temperature during a series of years, at Vera Cruz for example, we have some years marked by a very considerable mortality —*e.g.*, 1875, 1881—and others in which but few cases occur, even during the hottest part of the season—*e.g.*, 1869, 1870, 1879. Again, it happens that after a summer of almost complete exemption an epidemic is developed in the autumn which runs through the entire winter (1880–81). An important factor, which does not usually appear in statistical tables, relates to the number of susceptible individuals present at different times. The arrival, for example, of emigrants or of bodies of unacclimated troops at Havana or Vera Cruz would almost inevitably be followed by a marked increase in the mortality from yellow fever.

"Although the development of an epidemic seems to require a comparatively high temperature (75° to 80°), experience shows that it may continue in full force at a much lower temperature (60° to 70°), when local conditions are favorable and a susceptible population is exposed in the infected area. . . .

"Another factor of importance in the etiology of yellow-fever epidemics is atmospheric *moisture* and *precipitation*. Yellow fever is a disease of the seacoast, and of the margins of great rivers, and it does not prevail in arid, desert places in the interior, although the elevation may be but little above the sea level, and the temperature extremely high. There is reason to think that this difference is largely due to the difference as to moisture in the atmosphere and in the soil. Some authorities have insisted especially upon the presence of moisture in the atmosphere almost to the point of saturation, as an essential condition for the development of an epidemic. But, on the other hand, epidemics have sometimes occurred in unusually dry seasons, as at New Orleans in 1841. In Martinique, according to Dutrouleau, yellow fever has sometimes committed its greatest ravages after and during the dryest season.

"*Heavy rains*, by purifying the air and cleansing the streets and sewers of an infected city, exercise a favorable effect upon its sanitary condition, and in the tropics the commencement of the rainy season often puts an end to the prevailing epidemic. It is probable that the statement made by some authors, that upon the coast of Guiana, and elsewhere in the tropics, dry weather is favorable to the spread of the disease, is but another way of stating the fact that the heavy rains of tropical regions are unfavorable, the dry weather being only dry by comparison."

Scientific Researches Relating to the Etiology of Yellow Fever.—The present writer, as a member of the Havana Yellow-Fever Commission, in 1879, made the first systematic attempt to solve the unsettled questions relating to yellow-fever etiology by modern methods of research.

Naturally the first and most important question to engage my attention was that relating to the specific infectious agent, or "germ," which there was every reason to believe must be found in the bodies of infected individuals. Was this germ present in the blood, as in the case of relapsing fever; or was it to be found in the organs and tissues which upon post-mortem examination give evidence of pathological changes, as in typhoid fever, pneumonia, and diphtheria; or was it to be found in the alimentary canal, as in cholera and dysentery? The clinical history of the disease indicated a general blood infection. As my equipment included the best microscopical apparatus made, I had strong hopes that in properly stained preparations of blood taken from the circulation of yellow-fever patients my Zeiss $\frac{1}{18}$ oil-immersion objective would reveal to me the germ I was in search of. But I was doomed to disappointment. Repeated examinations of blood from patients in every stage of the disease failed to demonstrate the presence of microorganisms of any kind. My subsequent investigations in Havana, Vera Cruz, and Rio de Janeiro, made in 1887, 1888, and 1889, were equally unsuccessful. And numerous competent microscopists of various nations have since searched in vain for this elusive germ. Another method of attacking this problem consists in introducing blood from yellow-fever patients or recent cadavers into various "culture media" for the purpose of cultivating any germ that might be present. Extended researches of this kind also gave a negative result, which in my final report I stated as follows: "The specific cause of yellow fever has not yet been demonstrated. It is demonstrated that microorganisms, capable of development in the culture media usually employed by bacteriologists, are found in the blood and tissues of yellow-fever cadavers only in exceptional cases, when cultures are made very soon after death."

Since this report was made various investigators have attacked the question of yellow-fever etiology, and one of them has made very positive claims to the discovery of the specific germ. I refer to the Italian bacteriologist, Sanarelli. His researches were made in Brazil, and, singularly enough, he found in the blood of the first case examined by him a bacillus. It was present in large numbers, but this case proved to be unique, for neither Sanarelli nor any one else has since found it in such abundance. It has been found in small numbers in the blood and tissues of yellow-fever cadavers in a certain number of the cases examined. But carefully conducted researches by competent bacteriologists have failed to demonstrate its presence in a considerable proportion of the cases, and the recent researches of Reed, Carroll, and Agramonte demonstrate conclusively that the bacillus of Sanarelli has nothing to do with the etiology of yellow fever.

So far as I am aware, Dr. Carlos Finlay, of Havana, Cuba, was

the first to suggest the transmission of yellow fever by mosquitos. In a communication made to the Academy of Sciences of Havana, in October, 1881, he gave an account of his first attempts to demonstrate the truth of his theory. In a paper contributed to the *Edinburgh Medical Journal* in 1894 Dr. Finlay gives a summary of his experimental inoculations up to that date as follows:

"A summary account of the experiments performed by myself (and some also by my friend, Dr. Delgado), during the last twelve years, will enable the reader to judge for himself. The experiment has consisted in first applying a captive mosquito to a yellow-fever patient, allowing it to introduce its lance and to fill itself with blood; next, after the lapse of two or more days, applying the same mosquito to the skin of a person who is considered susceptible to yellow fever; and, finally, observing the effects, not only during the first few weeks, but during periods of several years, so as to appreciate the amount of immunity that should follow.

"Between the 30th of June, 1881, and the 2d of December, 1893, eighty-eight persons have been so inoculated. All were white adults, uniting the conditions which justify the assumption that they were susceptible to yellow fever. Only three were women. The chronological distribution of the inoculations was as follows: Seven in 1881, 10 in 1883, 9 in 1885, 3 in 1886, 12 in 1887, 9 in 1888, 7 in 1889, 10 in 1890, 8 in 1891, 3 in 1892, and 10 in 1893.

"The yellow-fever patients upon whom the mosquitos were contaminated were, almost in every instance, well-marked cases of the albuminuric or melano-albuminuric forms, in the second, third, fourth, fifth, or sixth day of the disease. In some of the susceptible subjects, the inoculation was repeated when the source of the contamination appeared uncertain.

"Among the eighty-seven who have been under observation, the following results have been recorded: Within a term of days, varying between five and twenty-five after the inoculation, *one* presented a mild albuminuric attack, and *thirteen only* 'acclimation fevers.'"

While Finlay's theory appeared to be plausible and to explain many of the facts relating to the etiology of yellow fever, his experimental inoculations not only failed to give it substantial support, but the negative results, as reported by himself, seemed to be opposed to the view that yellow fever is transmitted by the mosquito. It is true that he reports one case which "presented a mild albuminuric attack" which we may accept as an attack of yellow fever. But in view of the fact that this case occurred in the city of Havana, where yellow fever is endemic, and of the eighty-six negative results from similar inoculations, the inference seemed justified that in this case the disease was contracted in some other way than as a result of the so-called

"mosquito inoculation." The thirteen cases in which "only acclimation fevers" occurred "within a term of days varying between five and twenty-five after the inoculation" appeared to me to have no value as giving support to Finlay's theory; first, because these "acclimation fevers" could not be identified as mild cases of yellow fever; second, because the ordinary period of incubation in yellow fever is less than five days; and, third, because these individuals, having recently arrived in Havana, were liable to attacks of yellow fever, or of "acclimation fever" as a result of their residence in this city and quite independently of Dr. Finlay's mosquito inoculations. For these reasons Dr. Finlay's experiments failed to convince the medical profession generally of the truth of his theory relating to the transmission of yellow fever, and this important question remained in doubt and a subject of controversy.

I became some time since impressed with the view that probably in yellow fever, as in the malarial fevers, there is an "intermediate host." I therefore suggested to Dr. Reed, president of the board,* appointed upon my recommendation for the study of this disease in the island of Cuba, that he should give special attention to the possibility of transmission by some insect, although the experiments of Finlay seemed to show that this insect was not a mosquito of the genus *Culex*, such as he had used in his inoculation experiments. I also urged that efforts should be made to ascertain definitely whether the disease can be communicated from man to man by blood inoculations. Evidently if this is the case the blood must contain the living infectious agent upon which the propagation of the disease depends, notwithstanding the fact that all attempts to demonstrate the presence of such a germ in the blood, by means of the microscope and culture methods, had proved unavailing. I had previously demonstrated by repeated experiments that inoculations of yellow-fever blood into lower animals—dogs, rabbits, guinea-pigs—give a negative result, but this negative result might well be because these animals were not susceptible to the disease and could not be accepted as showing that the germ of yellow fever was not present in the blood. A single inoculation experiment on man had been made in my presence in the city of Vera Cruz, in 1887, by Dr. Daniel Ruiz, who was in charge of the civil hospital in that city. But this experiment was inconclusive for the reason that the patient from whom the blood was obtained was in the eighth day of the disease, and it was quite possible that the specific germ might have been present at an earlier period and that after a certain number of days the natural

* The members of the board were: Major Walter Reed, Surgeon U. S. A.; Dr. James Carroll, Contract Surgeon U. S. A.; Dr. A. Agramonte, Contract Surgeon U. S. A., and Dr. Jesse W. Lazear, Contract Surgeon U. S. A.

resources of the body are sufficient to effect its destruction, or in some way to cause its disappearance from the circulation.

This was the status of the question of yellow-fever etiology when Dr. Reed and his associates commenced their investigations in Cuba during the summer of 1900. In a "Preliminary Note," read at the meeting of the American Public Health Association, October 22d, 1900, the board gave a report of three cases of yellow fever which they believed to be the direct result of mosquito inoculations. Two of these were members of the board, viz., Dr. Jesse W. Lazear and Dr. James Carroll, who voluntarily submitted themselves to the experiment. Dr. Carroll suffered a severe attack of the disease and recovered, but Dr. Lazear fell a victim to his enthusiasm in the cause of science and humanity. His death occurred on September 25th, after an illness of six days' duration. About the same time nine other individuals who volunteered for the experiment were bitten by infected mosquitos—*i.e.*, by mosquitos which had previously been allowed to fill themselves with blood from yellow-fever patients—and in these cases the result was negative. In considering the experimental evidence thus far obtained, the attention of the members of the board was attracted by the fact that in the nine inoculations with a negative result, "the time elapsing between the biting of the mosquito and the inoculation of the healthy subject varied in seven cases from two to eight days and in the remaining two from ten to thirteen days, whereas in two of the three successful cases the mosquito had been kept for twelve days or longer."

The inference drawn by Dr. Reed and his associates, from the experiments thus far made, was that yellow fever may be transmitted by mosquitos of the genus *Culex*, but that in order to convey the infection to a non-immune individual the insect must be kept for twelve days or longer after it has filled itself with blood from a yellow-fever patient in the earlier stages of the disease. In other words, that a certain period of incubation is required in the body of the insect before the germ reaches its salivary glands, and consequently before it is able to inoculate an individual with the germs of yellow fever. This inference, based upon experimental data, received support from other observations, which have been repeatedly made, with reference to the introduction and spread of yellow fewer in localities favorable to its propagation. When a case is imported into one of our Southern seaport cities from Havana, Vera Cruz, or some other endemic focus of the disease, an interval of two weeks or more occurs before secondary cases are developed as a result of such importation. In the light of our present knowledge this is readily understood. A certain number of mosquitos having filled themselves with blood from this first case after an interval of twelve days or more bite non-immune individuals living

in the vicinity, and these individuals after a brief period of incubation fall sick with the disease; being bitten by other mosquitos they serve to transmit the disease through the "intermediate host" to still others. Thus the epidemic extends, at first slowly as from house to house, then more rapidly, as by geometrical progression.

It will be seen that the essential difference between the successful experiments of the board of which Dr. Reed is president and the unsuccessful experiments of Finlay consists in the length of time during which the mosquitos were kept after filling themselves with blood from a yellow-fever patient. In Finlay's experiments the interval was usually short—from two to five or six days, and it will be noted that in the experiments of Reed and his associates the result was invariably negative when the insect had been kept for less than eight days (seven cases).

Having obtained what they considered satisfactory evidence that yellow fever is transmitted by mosquitos, Dr. Reed and his associates proceeded to extend their experiments for the purpose of establishing the fact in such a positive manner that the medical profession and the scientific world generally might be convinced of the reliability of the experimental evidence upon which their conclusions were based. These conclusions, which have been fully justified by their subsequent experiments were stated in their "Preliminary Note" as follows:

"1. Bacillus icteroides (Sanarelli) stands in no causative relation to yellow fever, but, when present, should be considered as a secondary invader in this disease.

"2. The mosquito serves as the intermediate host for the parasite of yellow fever."

"An Additional Note" read at the Pan-American Medical Congress held in Havana, Cuba, February 4th–7th, 1901, contains a report of the further experiments made up to that date.

In summing up their results at the conclusion of this report the following statement is made:

"Out of a total of eighteen non-immunes whom we have inoculated with contaminated mosquitos, since we began this line of investigation, eight, or 44.4 per cent., have contracted yellow fever. If we exclude those individuals bitten by mosquitos that had been kept less than twelve days after contamination, and which were therefore probably incapable of conveying the disease, we have to record eight positive and two negative results—eighty per cent."

In a still later report (May, 1901) Dr. Reed says: "We have thus far succeeded in conveying yellow fever to twelve individuals by means of the bites of contaminated mosquitos."

The experiments already referred to show in the most conclusive manner that the blood of yellow-fever patients contains the infectious

agent, or germ, to which the disease is due, and this has been further demonstrated by direct inoculations from man to man. This experiment was made by Dr. Reed at "Camp Lazear" upon four individuals, who freely consented to it; and in three of the four a typical attack of yellow fever resulted from the blood injection. The blood was taken from a vein at the bend of the elbow on the first or second day of sickness and was injected subcutaneously into the four non-immune individuals, the amount being in one positive case 2 c.c., in one 1.5 c.c., and in one 0.5 c.c. In the case attended with a negative result, a Spanish immigrant, a mosquito inoculation also proved to be without effect, and Dr. Reed supposes that this individual "probably possesses a natural immunity to yellow fever." Dr. Reed says with reference to these experiments: "It is important to note that in the three cases in which the injection of the blood brought about an attack of yellow fever, careful culture from the same blood, taken immediately after injection, failed to show the presence of Sanarelli's bacillus."

Having demonstrated the fact that yellow fever is propagated by mosquitos Dr. Reed and his associates have endeavored to ascertain whether it may also be propagated, as has been commonly supposed, by clothing, bedding, and other articles which have been in use by those sick with this disease. With reference to the experiments made for the solution of this question I cannot do better than to quote *in extenso* from Dr. Reed's paper read at the Pan-American Medical Congress in Havana. He says:

"We believe that the general consensus of opinion both of the medical profession and of the laity is strongly in favor of the conveyance of yellow fever by fomites. The origin of epidemics, devastating in their course, has been frequently attributed to the unpacking of trunks and boxes that contained supposedly infected clothing; and hence the efforts of health authorities, both state and national, are being constantly directed to the thorough disinfection of all clothing and bedding shipped from ports where yellow fever prevails. To such extremes have efforts at disinfection been carried, in order to prevent the importation of this disease into the United States, that, during the epidemic season, all articles of personal apparel and bedding have been subjected to disinfection, both at the port of departure and at the port of arrival; and this has been done whether the articles have previously been contaminated by contact with yellow-fever patients or not. The mere fact that the individual has resided, even for a day, in a city where yellow fever is present, has been sufficient cause to subject his baggage to rigid disinfection by the sanitary authorities.

"To determine, therefore, whether clothing and bedding which have been contaminated by contact with yellow-fever patients and their discharges can convey this disease is a matter of the utmost im-

portance. Although the literature contains many references to the failure of such contaminated articles to cause the disease, we have considered it advisable to test, by actual experiment on non-immune human beings, the theory of the conveyance of yellow fever by fomites since we know of no other way in which this question can ever be finally determined.

"For this purpose there was erected at Camp Lazear a small frame house consisting of one room fourteen by twenty feet and known as 'Building No. 1,' or the 'Infected Clothing and Bedding Building.' The cubic capacity of this house was twenty-eight hundred feet. It was tightly ceiled within with 'tongue-and-grooved' boards, and was well battened on the outside. It faced to the south and was provided with two small windows, each twenty by thirty-four inches in size. These windows were both placed on the south side of the building, the purpose being to prevent, as much as possible, any thorough circulation of the air within the house. They were closed by permanent wire screens of 0.5 mm. mesh. In addition sliding glass sashes were provided within and heavy wooden shutters without; the latter intended to prevent the entrance of sunlight into the building, as it was not deemed desirable that the disinfecting qualities of sunlight, direct or diffused, should at any time be exerted on the articles of clothing contained within this room. Entrance was effected through a small vestibule, three by five feet, also placed on the southern side of the house. This vestibule was protected without by a solid door and was divided in its middle by a wire screen door, swung on spring hinges. The inner entrance was also closed by a second wire screen door. In this way the passage of mosquitos into this room was effectually excluded. During the day, and until after sunset, the house was kept securely closed, while by means of a suitable heating apparatus the temperature was raised to 92° to 95° F. Precaution was taken at the same time to maintain a sufficient humidity of the atmosphere. The average temperature of this house was thus kept at 76.2° F. for a period of sixty-three days.

"November 30th, 1900, the building now being ready for occupancy, three large boxes filled with sheets, pillow-slips, blankets, etc., contaminated by contact with cases of yellow fever and their discharges were received and placed therein. The majority of the articles had been taken from the beds of patients sick with yellow fever at Las Animas Hospital, Havana, or at Columbia Barracks. Many of them had been purposely soiled with a liberal quantity of black vomit, urine, and fecal matter. A dirty comfortable and a much-soiled pair of blankets, removed from the bed of a patient sick with yellow fever in the town of Quemados, were contained in one of these boxes. The same day, at 6 P.M., Dr. R. P. Cooke, Acting Assistant Surgeon U.

S. A., and two privates of the hospital corps, all non-immune young Americans, entered this building and deliberately unpacked these boxes, which had been tightly closed and locked for a period of two weeks. They were careful at the same time to give each article a thorough handling and shaking, in order to disseminate through the air of the room the specific agent of yellow fever, if contained in these fomites. These soiled sheets, pillow-cases, and blankets were used in preparing the beds in which the members of the hospital corps slept. Various soiled articles were hung around the room and placed about the bed occupied by Dr. Cooke.

"From this date until December 19th, 1900, a period of twenty days, this room was occupied each night by these three non-immunes. Each morning the various soiled articles were carefully packed in the aforesaid boxes, and at night again unpacked and distributed about the room. During the day the residents of this house were permitted to occupy a tent pitched in the immediate vicinity, but were kept in strict quarantine.

"December 12th a fourth box of clothing and bedding was received from Las Animas Hospital. These articles had been used on the beds of yellow-fever patients, but in addition had been purposely soiled by the bloody stools of a fatal case of this disease. As this box had been packed for a number of days, when opened and unpacked by Dr. Cooke and his assistants, on December 12th, the odor was so offensive as to compel them to retreat from the house. They pluckily returned, however, within a short time and spent the night as usual.

"December 19th these three non-immunes were placed in quarantine for five days and then given the liberty of the camp. All had remained in perfect health, notwithstanding their stay of twenty nights amid such unwholesome surroundings.

"During the week December 20th–27th, the following articles were also placed in this house, viz., pajama suit, 1; undershirts, 2; nightshirts, 4; pillow-slips, 4; sheets, 6; blankets, 5; pillows, 2; mattresses, 1. These articles had been removed from the persons and beds of four patients sick with yellow fever and were very much soiled, as any change of clothing or bed-linen during their attacks had been purposely avoided, the object being to obtain articles as thoroughly contaminated as possible.

"From December 21st, 1900, till January 10th, 1901, this building was again occupied by two non-immune young Americans, under the same conditions as the preceding occupants, except that these men slept every night in the very garments worn by yellow-fever patients throughout their entire attacks, besides making use exclusively of their much-soiled pillow-slips, sheets, and blankets. At the end of twenty-one nights of such intimate contact with these fomites, they

also went into quarantine, from which they were released five days later in perfect health.

"From January 11th till January 31st, a period of twenty days, 'Building No. 1' continued to be occupied by two other non-immune Americans, who, like those who preceded them, have slept every night in the beds formerly occupied by yellow-fever patients and in the night-shirts used by these patients throughout the attack, without change. In addition, during the last fourteen nights of their occupancy of this house they have slept, each night, with their pillows covered with towels that had been thoroughly soiled with the blood drawn from both the general and capillary circulation, on the first day of the disease, in the case of a well-marked attack of yellow fever. Notwithstanding this trying ordeal, these men have continued to remain in perfect health.

"The attempt which we have therefore made to infect 'Building No. 1,' and its seven non-immune occupants, during a period of sixty-three days, has proved an absolute failure. We think we cannot do better here than to quote from the classic work of La Roche. This author says: 'In relation to the yellow fever, we find so many instances establishing the fact of the non-transmissibility of the disease through the agency of articles of the kind mentioned, and of merchandise generally, that we cannot but discredit the accounts of a contrary character assigned in medical writings, and still more to those presented on the strength of popular report solely. For if, in a large number of well-authenticated cases, such articles have been handled and used with perfect impunity—and that, too, often under circumstances best calculated to insure the effect in question—we have every reason to conclude that a contrary result will not be obtained in other instances of a similar kind; and that consequently the effect said to have been produced by exposure to those articles, must—unless established beyond the possibility of doubt—be referred to some other agency.'"

Having demonstrated the fact that yellow fever is transmitted by a certain species of mosquito and that the infectious agent is in the blood of those sick with the disease, Major Reed and his associates naturally devoted themselves to a search for a living germ by microscopical examination of the blood and of infected mosquitos. So far they have been unsuccessful, and apparently this failure is due to the fact that in the disease under consideration we have to deal with an ultra-microscopic microorganism. This inference is sustained by recent experiments made by Dr. Carroll, a member of the board heretofore referred to, in the vicinity of Havana. In these experiments blood taken from the circulation of a yellow-fever patient was passed through a Berkefeldt filter and a small quantity of the filtrate

injected under the skin of two non-immune individuals who volunteered for the experiment. Both fell sick within the usual period of incubation and suffered typical attacks of yellow fever.

The writer, in the "Preliminary Report of the Havana Yellow Fever Commission" (1879), says: "The patients from whom specimens of blood were obtained were mostly soldiers in the military hospital of San Ambrosio. Ninety-eight specimens, from forty-one undoubted cases of yellow fever, were carefully studied, and one hundred and five photographic negatives were made which show satisfactorily everything demonstrable by the microscope. These photographs were mostly made with a magnifying power of fourteen hundred and fifty diameters, obtained by the use of Zeiss' one-eighteenth-inch objective and Tolles' amplifier. Probably no better lens than the Zeiss one-eighteenth (oil immersion) could have been obtained for this work, and it is doubtful whether any objective has ever been made capable of showing more than is revealed by this magnificent lens. With the power used, organisms much smaller than those described as existing in the blood of anthrax or of relapsing fever would be clearly defined.

"If there is any microorganism in the blood of yellow fever, demonstrable by the highest powers of the microscope as at present perfected, the photomicrographs taken in Havana should show it. *No such organism is shown in any preparation photographed immediately after collection.*"

Subsequent repeated examinations of specimens obtained in Havana, Vera Cruz, and Rio de Janeiro, and stained by various methods, gave a similar result.

This failure to find any microorganism in the blood led the writer some time since to suggest the possibility that the yellow-fever germ is ultra-microscopic. Some years since Loeffler and Frosch demonstrated the fact that the infectious element of foot-and-mouth disease (of cattle and sheep) passes through a porcelain filter, the virulence of the filtrate having been proved by inoculation experiments. This possibility should be kept in view in future researches relating to the etiology of infectious diseases in which the presence of a parasitic microorganism has not been demonstrated—*e.g.*, smallpox and syphilis.

In fatal cases of yellow fever there is, as a rule, a passive hemorrhage into the stomach and intestines and the vomited matter and dejecta contain more or less blood. Unless, therefore, the germ present in the blood in the earlier stages of the disease is in some manner destroyed it should be found in the dark-colored alvine discharges after such passive hemorrhage has occurred, and clothing and bedding soiled with such discharges would be likely to play an important part in the propagation of the disease. This has been generally assumed to be the case and in papers heretofore published the present writer has in-

sisted upon the disinfection of fæces and of soiled articles of clothing and bedding. But the experiments of Reed and Carroll, above referred to, give no support to this view and the inference from these experiments is that the germ quickly perishes and is not present in a living and active condition in the bloody discharges from the bowels. We cannot, however, regard this matter as definitely and finally settled. As the experiments made show only one way of transmission, viz., by inoculation, it seems possible that a living germ might be present in the alvine discharges, but that the disease is not propagated by means of these discharges because there is no ordinary means by which it could find its way to the circulation of a susceptible individual. We have no evidence that the disease is ever transmitted by way of the digestive tract, in food or water, as is the case with cholera and typhoid fever, in which diseases the germ is known to be present in the discharges from the bowels.

Prophylaxis.

It is evident that in view of our present knowledge relating to the mode of transmission of yellow fever, the preventive measures which have heretofore been considered most important—isolation of the sick, disinfection of clothing and bedding, and municipal sanitation—are either of no avail or of comparatively little value. It is true that yellow-fever epidemics have resulted, as a rule, from the introduction to a previously healthy locality of one or more persons suffering from the disease. But we now know that its extension did not depend upon the direct contact of the sick with non-immune individuals and that isolation of the sick from such contact is unnecessary and without avail. On the other hand, complete isolation from the agent which is responsible for the propagation of the disease is all-important. In the absence of a yellow-fever patient from which to draw blood the mosquito is harmless, and in the absence of the mosquito the yellow-fever patient is harmless—as the experimental evidence now stands. Yellow-fever epidemics are terminated by cold weather because then the mosquitos die or become torpid. The sanitary condition of our Southern seaport cities is no better in winter than in summer, and if the infection attached to clothing and bedding it is difficult to understand why the first frosts of autumn should arrest the progress of an epidemic. But all this is explained now that the mode of transmission has been demonstrated.

Insanitary local conditions may, however, have a certain influence in the propagation of the disease, for it has been ascertained that the species of mosquito which serves as an intermediate host for the yellow-fever germ may breed in cesspools and sewers, as well as in stag-

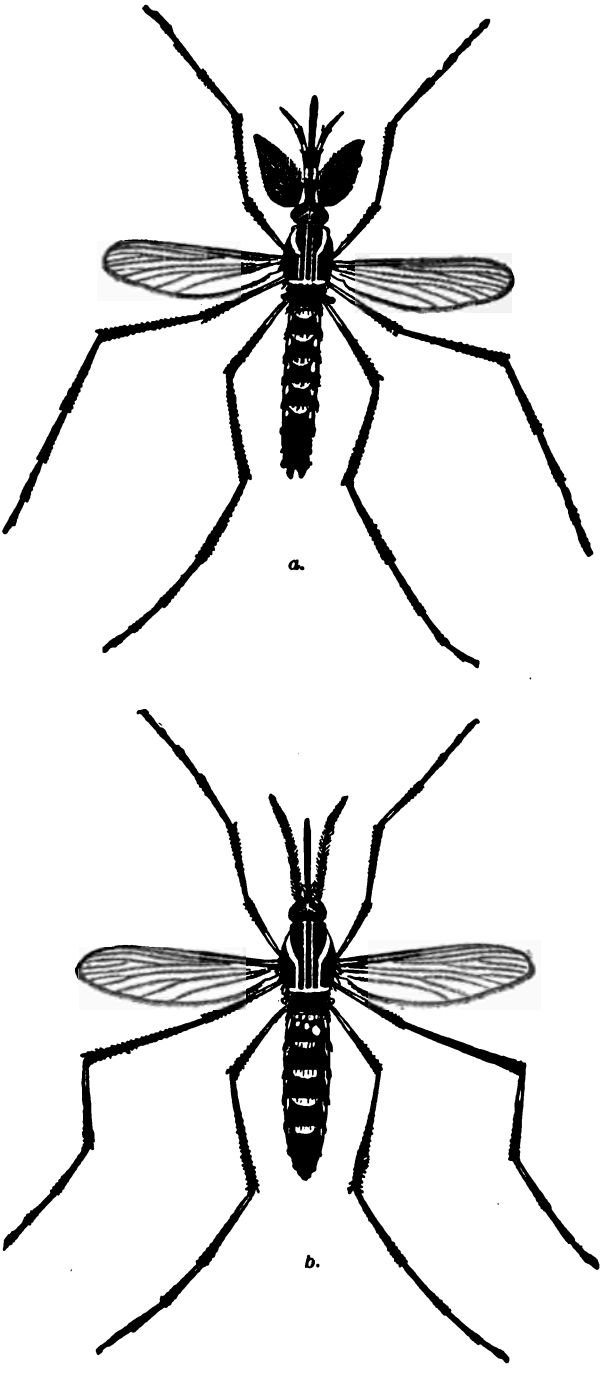


FIG. 41.—Adult Stegomyia fasciata. *a*, Male; *b*, female.

nant pools of water. If, therefore, the streets of a city are unpaved and ungraded and there are open spaces where water may accumulate in pools, as well as open cesspools to serve as breeding places for *Stegomyia*,* that city will present conditions more favorable for the propagation of yellow fever than it would if well paved and drained and sewered.

The question whether yellow fever may be transmitted by any other species of mosquito than *Stegomyia* has not been determined. Facts relating to the propagation of the disease indicate that the mosquito which serves as an intermediate host for the yellow-fever germ has a somewhat restricted geographical range and is to be found especially upon the seacoast and the margins of rivers in the so-called "yellow-fever zone."

It must not be supposed that *Stegomyia* is found only where yellow fever prevails. The propagation of the disease depends upon the introduction of an infected individual to a locality where this mosquito is found, at a season of the year when it is active. Owing to the short period of incubation (five days or less), the brief duration of the disease, and especially of the period during which the infectious agent (germ) is found in the blood, it is evident that ships sailing from infected ports, upon which cases of yellow fever develop, are not likely to introduce the disease to distant seaports. The continuance of an epidemic on ship-board, as on the land, must depend upon the presence of infected mosquitos and of non-immune individuals. Under these circumstances we can readily understand why the disease should not be carried from the West Indies or from South America to the Mediterranean, to the east coast of Africa, or to Asiatic seaport cities. On the other hand, if the disease could be transmitted by infected clothing, bedding, etc., there seems no good reason why it should not have been carried to these distant localities long ago.

The restriction as regards altitude probably depends upon the fact that the mosquito which serves as an intermediate host is a coast species, which does not live in elevated regions. It is a well-established fact that yellow fever has never prevailed in the city of Mexico, although this city has constant and unrestricted intercourse with the infected seaport, Vera Cruz. Persons who have been exposed in Vera Cruz during the epidemic season frequently fall sick after their arrival in the city of Mexico, but they do not communicate the disease to those in attendance upon them or to others in the vicinity. Evidently some factor essential for the propagation of the disease is absent, although we have the sick man, his clothing and bedding, and the insanitary

* Theobold, the English entomologist, has taken *Culex fasciatus* from the genus *Culex* and placed it in a new genus—*Stegomyia*.

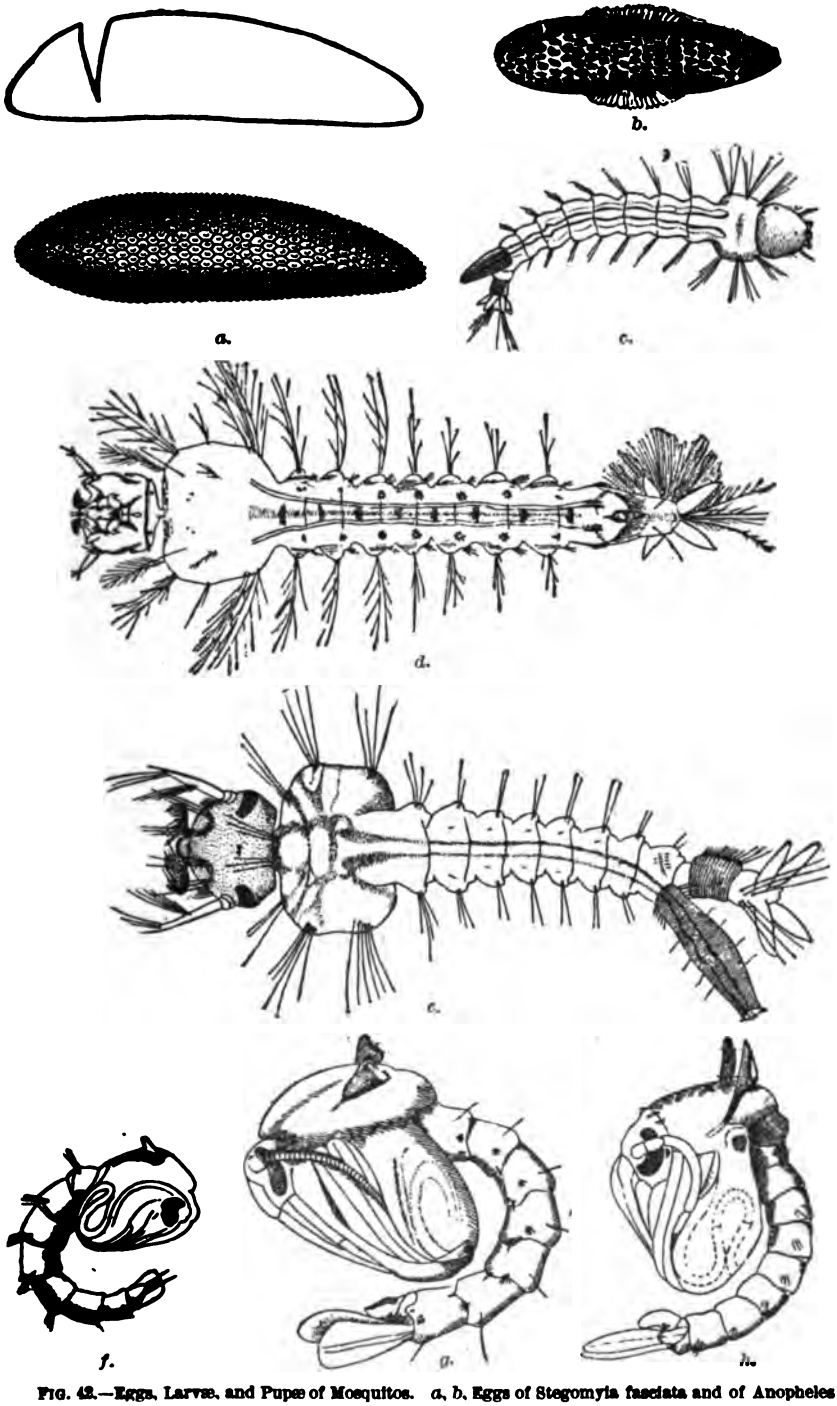


FIG. 42.—Eggs, Larvæ, and Pupæ of Mosquitos. *a*, *b*, Eggs of Stegomyia fasciata and of Anopheles maculipennis; *c*, *d*, *e*, larvæ of Stegomyia fasciata, Anopheles maculipennis, and Culex pungens; *f*, *g*, *h*, pupæ of Stegomyia fasciata, Anopheles maculipennis, and Culex pungens.

local conditions which have been supposed to constitute an essential factor. I am not aware that any observations have been made with reference to the presence or absence of *Stegomyia* in high altitudes, but the inference that it is not to be found in such localities as the city of Mexico seems justified by the established facts already referred to.

The proper measures of prophylaxis are given in the following circular, which was submitted for my approval by the chief surgeon, Department of Cuba, and was published by the commanding general of that department, who, until quite recently, was a member of the Medical Corps of the Army:

CIRCULAR, No. 5. } HEADQUARTERS DEPARTMENT OF CUBA, *Havana, April 27th, 1901.*

Upon the recommendation of the chief surgeon of the department, the following instructions are published and will be strictly enforced at all military posts in this department:

The recent experiments made in Havana by the Medical Department of the Army having proved that yellow fever, like malarial fever, is conveyed chiefly, and probably exclusively, by the bite of infected mosquitos, important changes in the measures used for the prevention and treatment of this disease have become necessary.

1. In order to prevent the breeding of mosquitos and to protect officers and men against their bites, the provisions of General Orders No. 6, Department of Cuba, December 21st, 1900, shall be carefully carried out, especially during the summer and fall.

2. So far as yellow fever is concerned, infection of a room or building simply means that it contains infected mosquitos, that is, mosquitos which have fed on yellow-fever patients. Disinfection, therefore, means the employment of measures aimed at the destruction of these mosquitos. The most effective of these measures is fumigation, with either sulphur, formaldehyde, or insect powder. The fumes of sulphur are the quickest and most effective insecticide but are otherwise objectionable. Formaldehyde gas is quite effective if the infected rooms are kept closed and sealed for two or three hours. The smoke of insect powder has also been proved very useful; it readily stupefies mosquitos, which drop to the floor and can then be easily destroyed.

The washing of walls, floors, ceilings, and furniture with disinfectants is unnecessary.

3. As it has been demonstrated that yellow fever cannot be conveyed by fomites, such as bedding, clothing, effects, and baggage, they need not be subjected to any special disinfection. Care should be taken, however, not to remove them from the infected rooms until after formaldehyde fumigation, so that they may not harbor infected mosquitos.

Medical officers taking care of yellow-fever patients need not be isolated; they can attend other patients and associate with non-immunes with perfect safety to the garrison. Nurses and attendants taking care of yellow-fever patients shall remain isolated, so as to avoid any possible danger of their conveying mosquitos from patients to non-immunes.

4. The infection of mosquitos is most likely to occur during the first two or three days of the disease. Ambulant cases, that is, patients not ill enough to take to their beds and remaining unsuspected and unprotected, are probably those most

responsible for the spread of the disease. It is therefore essential that all fever cases should be at once isolated and so protected that no mosquitos can possibly get access to them until the nature of the fever is positively determined.

Each post shall have a "reception ward" for the admission of all fever cases and an "isolation ward" for the treatment of cases which prove to be yellow fever. Each ward shall be made mosquito-proof by wire netting over doors and windows, a ceiling of wire netting at a height of seven feet above the floor, and mosquito bars over the beds. There should be no place in it where mosquitos can seek refuge, not readily accessible to the nurse. Both wards can be in the same building, provided they are separated by a mosquito-tight partition.

5. All persons coming from an infected locality to a post shall be kept under careful observation until the completion of five days from the time of possible infection, either in a special detention camp or in their own quarters; in either case their temperature should be taken twice a day during this period of observation, so that those who develop yellow fever may be placed under treatment at the very inception of the disease.

6. Malarial fever, like yellow fever, is communicated by mosquito bites and therefore is just as much of an infectious disease and requires the same measures of protection against mosquitos. On the assumption that mosquitos remain in the vicinity of their breeding places, or never travel far, the prevalence of malarial fever at a post would indicate want of proper care and diligence on the part of the surgeon and commanding officer in complying with General Orders No. 6, Department of Cuba, 1900.

7. Surgeons are again reminded of the absolute necessity, in all fever cases, to keep, from the very beginning, a complete chart of pulse and temperature, since such a chart is their best guide to a correct diagnosis and the proper treatment.

By command of Major-General Wood,

H. L. SCOTT,
Adjutant-General.

The results obtained in the city of Havana by applying in a practical way the knowledge gained by Major Reed and his associates with reference to the transmission of yellow fever are given by Major Gorgas, Surgeon U. S. A., in his reports as chief sanitary officer of that city. I quote from his report for November, 1901:

"During the month we have had no cases and no deaths from yellow fever. This can be said of no preceding November since 1762. Taking this month for the last eleven years, the maximum number of deaths from this disease occurred in 1896, when we had 244; the minimum in 1898, when we had 13; average, 48.

"If we take the yellow-fever year as beginning the 1st of April and consider the same eleven years, it will be seen that the maximum number of deaths, 1,115, occurred in 1896, and the minimum, 79, in 1899; average, 410. This year, for the same period, we have had only five deaths.

"Last year, 1900, we had, during this month, 214 cases and 54 deaths. This year the last case of yellow fever occurred on September 28th; that is, we have gone over two months without a single case or death belonging to Havana.

"I consider this a demonstration that Havana has at last been freed from the infection of yellow fever.

"It must be remembered that October and November are the months when yellow fever is rife in Havana, and that, for the past century, there has never been a day during these two months when there were not many cases of yellow fever in the city; and very few years can be picked out, in all this time, in which the record for each day during these months does not show several deaths.

"This result I consider due to the system, introduced last February, of killing infected mosquitos in the neighborhood of each point of infection as it developed.

"The body of the report will show the large amount of work done with regard to the destruction of the mosquito. Mr. Le Prince, who is in charge of this work, estimates that the mosquitos in the city are only about one-tenth as numerous this November as they were last November, and I am inclined to think that this is not an exaggerated statement, but of course it is hard to substantiate. At certain places, for reasons not yet discovered, they are just as bad as they were last year, but in a great many places in the city where they were very bad last year, they have almost entirely disappeared."

The success which has been obtained at the New Orleans Quarantine station in the *disinfection of ships* by sulphur dioxide can be readily understood in the light of our present knowledge. This agent would quickly destroy infected mosquitos in the hold of a ship or in cabins that had been occupied by yellow-fever patients. Under the theory that the danger was attached to the cargo of the ship or the baggage of passengers, the efficacy of the method was open to question. Either sulphur dixoide or formaldehyde gas may be used for the destruction of mosquitos in infected rooms on shipboard or on shore. And, so far as can at present be determined upon the basis of experimental evidence, no other disinfection is necessary.

Susceptibility.

Individuals of every race and of all ages, who are exposed to infection for the first time, during the epidemic prevalence of the disease, are subject to be attacked. But there is a wide difference in the degree of this susceptibility among races, and among individuals of the same race.

Race.—It has been asserted that the negro race has a congenital immunity from yellow fever, but this is a mistake. The susceptibility of the negro is, however, much less than that of the white race, and among those attacked the mortality, as a rule, is small. This is shown by the statistics relating to white and black troops in the British ser-

vice at West India stations. "While in Jamaica the annual loss among the former amounts to 102 per 1,000 of the mean strength, the deaths among the blacks did not exceed 8 per 1,000. In the Bahamas the mortality of the whites was 59 in 1,000, that of the blacks 5.6 in 1,000" (La Roche).

In general it may be stated that the natives of northern latitudes are more susceptible than those born in tropical or subtropical climates. Blair, who had an extended experience in Guiana, says: "The lower the winter temperature in the native country of those attacked, the more severe was their sickness, so that, while the mortality among West Indians amounted to only 6.9 per cent. of the sick, it rose to 17.1 among the Italians and French, 19.3 among the English, 20.2 among the Germans and Dutch, and 27.7 among Scandinavians and Russians."

Sex.—There is probably no difference in the susceptibility of the sexes, but males are attacked in greater proportion than females, because they more frequently, and often recklessly, visit infected localities. The mortality is, as a rule, considerably greater among males. Ligon, in giving an account of the pestilence at Barbadoes in 1647, of which he was an eye witness, says: "The cause was unknown; one could not say if the ships of commerce had imported the scourge, or if it came from bad food, marshy water, the intemperance of the colonists, and, above all, the great quantity of *eau-de-vie* which they drank. It was the most debauched who perished first, and not one woman died for ten men." No doubt Ligon was right in ascribing the difference in the mortality of the sexes largely to the difference in their habits, with reference to the use of *eau-de-vie*. Those who habitually use spirituous liquors are less likely to recover from an attack than the temperate, and a recent debauch is a recognized predisposing cause.

Age.—Infants and old persons enjoy a comparative immunity, due in part, no doubt, to the fact that they are less exposed than active individuals in middle life. Dr. Rush records the fact that he has "met with a violent case of the disease in a child of four months, and a moderate case in a child of only ten weeks" (La Roche). Very young infants, however, commonly escape, or suffer so mild an attack that the nature of the disease is not recognized. In cities like New Orleans, which have suffered repeated epidemics, the proportion of children attacked is often exceptionally large, because they constitute a large share of the unprotected population, having been born since the last epidemic.

Immunity is acquired by suffering an attack of the disease; this acquired immunity is not, however, absolute.

Second attacks no doubt occasionally occur, although this has been denied by some authors. Blair, whose experience was very great, says

that he does not believe there is an instance of a second attack after a month's perfect restoration to health. Other authors are equally positive in their statements. On the other hand, we have numerous authentic accounts of second attacks. Thus "Dr. Jackson states that in Spain, during the epidemic of 1820, twenty well-authenticated instances came within his knowledge of persons being attacked who had the disease before." Dr. Wragg, speaking of the epidemic in Charleston in 1854, reports the occurrence of second attacks in a number of instances, and says: "Six of these were so well proved as to admit of no doubt on the subject. Some of the patients were identified as having gone through the fever in this (the Roper) hospital in 1852, throwing up black vomit on both occasions" (La Roche). Dr. Rush has given evidence of the same kind, and says that a second attack was more common when the first had been comparatively mild.

It is a remarkable fact that the population of a large city like Havana, or Rio Janeiro, in which yellow fever has been endemic for a series of years, enjoys such a degree of immunity from the effects of the deadly germ that there is no interruption of business or pleasure at a time when strangers in the city are falling sick on every side. The development of an *epidemic* in these cities depends upon the presence of susceptible strangers in sufficient number to furnish a series of cases considered large enough to justify the use of the word. The presence of but few strangers during the epidemic season leads to the announcement that the disease is not epidemic, but that sporadic cases occur from time to time. Under exceptional circumstances, however, epidemics are developed in these endemic foci of the disease, in which those who, by birth or long residence, were supposed to be "acclimatized," furnish a certain quota to the general mortality. This has frequently occurred, for example, in the city of New Orleans, where yellow fever formerly prevailed almost annually, and where the creole population was supposed to enjoy an hereditary immunity.

Hinemann writes with reference to Vera Cruz: "Until lately the physicians and people of Vera Cruz supported with fanaticism the dogma that natives were absolutely exempt from yellow fever. But the fearful epidemics of recent years (1875, 1877, 1878) have worked a change; for so many native children and adults suffered, that the truth could no longer be denied that these do not enjoy an absolute immunity."

In Cuba, the dogma that creoles are exempt from yellow fever did not withstand the searching investigations made by the Havana Yellow-Fever Commission of 1879.

The truth appears to be that the so-called "acclimatization" of strangers or the immunity of the creole population in localities where the disease has established itself as an endemic malady is due

in nearly every instance to an unrecognized attack of the disease. Without doubt the immunity of creoles is to a large extent due to a comparatively mild attack suffered during childhood. Even a severe attack presenting all the characteristic symptoms is commonly called by some other name. The testimony of Dr. Navea, of San José de las Lajas, Cuba, an inland town some twenty miles southeast of Havana, is interesting in this connection. He states in his report to Dr. Chaillé, president of the Yellow-Fever Commission of 1879:

"We have here annually, in the practice of the three physicians, from twenty to thirty Cuban children, and from thirty to forty Cuban adults, attacked with bilious remittent fever which is popularly designated typhus. There is nothing whatever to constitute a differential diagnosis between this fever of the natives and the yellow fever of strangers. It is characterized by its hemorrhagic tendency, albuminuria, black vomit, and all the symptoms of yellow fever. It is so well marked that even when seen by the uneducated they exclaim 'vomito.' The treatment for the one is best for the other. We have never seen a second attack of this bilious remittent fever, nor one who had recovered from it attacked with yellow fever. If any one of us three physicians here sees this fever attack a native Cuban, we say 'bilious remittent fever,' and if it attacks a person not a native of Cuba we say 'yellow fever'; but at bottom it is the same disease; and we agree to call it bilious remittent fever in Cubans solely because these believe themselves exempt from yellow fever, and are so prejudiced that they would be alarmed if assured that their disease was really yellow fever."

Dowler, in discussing this question, says: "The exemption of the creoles of the city is a fact which every epidemic has confirmed; for example, take that of 1841, in which 1,800 died; 5 of whom only were natives of the city; 1 aged three weeks; 3, two years. In 1843, among 692 deaths from yellow fever, but 2 are certified as having been born in New Orleans. That many creole children had, during the epidemic of 1853, a fever—a slight fever—yellow fever if you please—known as such rather by the coexistence of the epidemic than from any severe symptoms among these children—a slight fever never yet described, having generally but one paroxysm, lasting from six hours to one, two, or three days, scarcely ever requiring medication. That a few of these cases acquired an alarming violence, and even proved fatal, is most true—most deplorable."

Period of Incubation.

It has long been recognized that the period of incubation in yellow fever is comparatively short, and it has generally been stated by the best recognized authorities as less than five days. The experiments

of Major Reed and his associates have given us definite data upon this point, which they have summed up as follows: "The period of incubation in thirteen cases of experimental yellow fever has varied from forty-one hours to five days and seventeen hours."

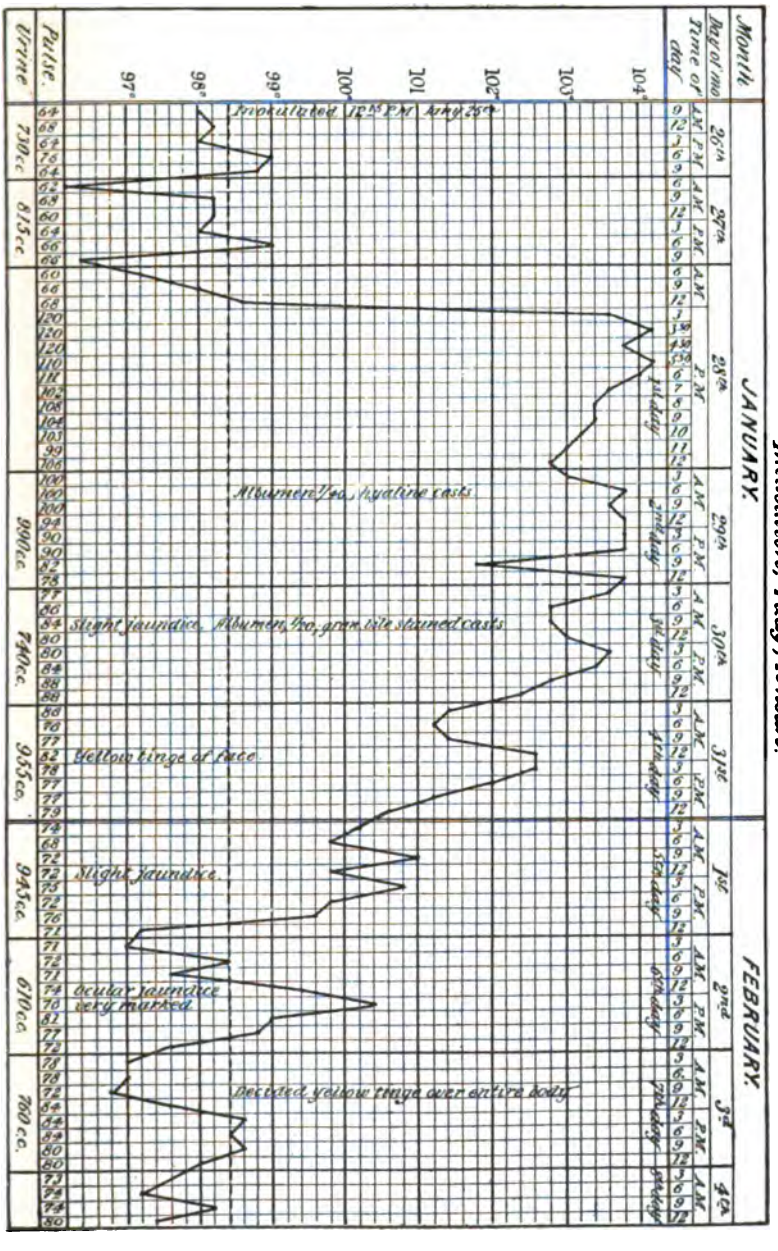
Clinical History.

As a rule, an attack of yellow fever is not preceded by any well-marked *premonitory symptoms*. The attack may occur at night in one who went to bed in his usual state of health, or in the early morning after an uninterrupted sleep, or during the day while engaged in ordinary occupations. In other cases there is a feeling of lassitude and discomfort for two or three days prior to the attack, with loss of appetite, slight pain in the back and loins, a feeling of giddiness or slight headache, flatulent eructations, constipation, a tendency to perspire at night, or upon very slight exertion, and more or less muscular debility, together with a disinclination for any mental exertion.

The attack is commonly inaugurated with a more or less decided *chill*, which by its violence and duration affords some indication of the probable severity of the case. In certain grave forms of the disease, however, the onset is insidious, and is not marked by any perceptible chill. In a considerable proportion of the mild cases, also, especially in the tropics, there is no rigor, and the patient experiences at most only a slight sensation of coldness, which quickly gives place to that of heat. If a thermometer is placed in the axilla during the initial chill it will be found that the temperature is already considerably above the normal, and very frequently it reaches the highest point attained during the entire attack within a few hours from its inception.

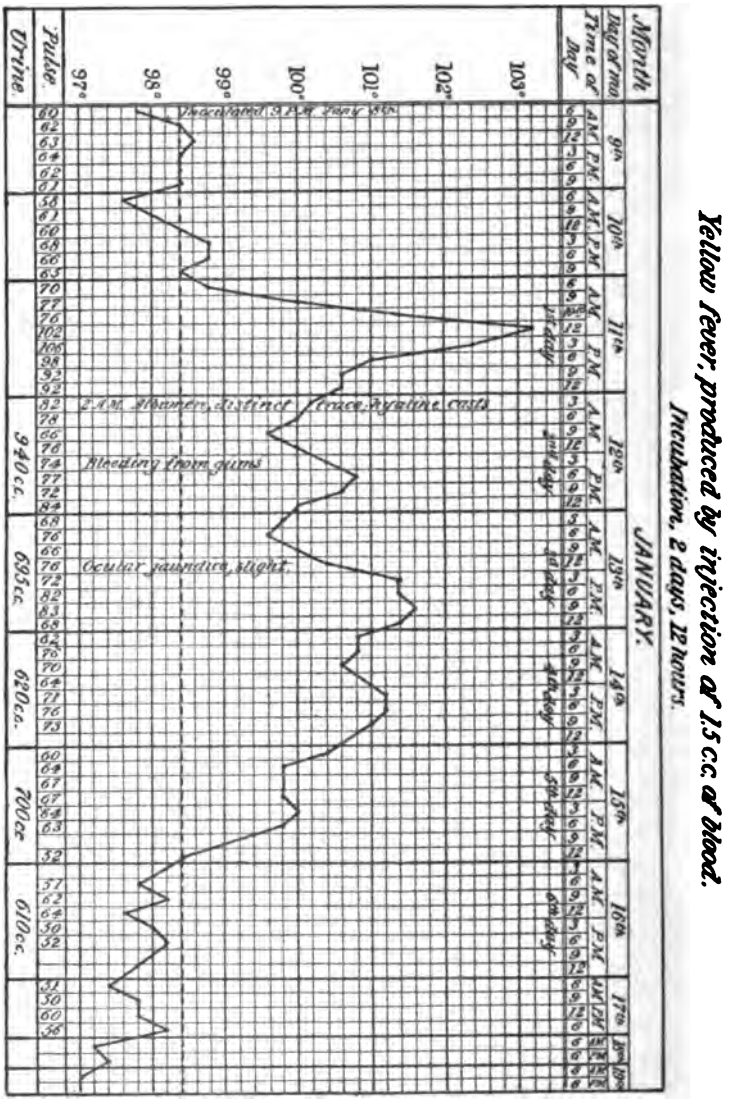
Accompanying the chill are other nervous phenomena, similar in kind to those attending the onset of other specific febrile diseases. There is *cephalalgia*, often very severe, and located by preference in the forehead and supraorbital region; the eyeballs also are painful, and there is intolerance of light in some instances. Pain in the loins is a very constant and early symptom, which occasions much distress, and sometimes extorts groans and cries from the patient. At the same time pain is usually experienced in the lower extremities, often of a very severe character, constituting the *coup de barre* of the French authors; it affects especially the calves of the legs, the knees, and the ankles. These symptoms continue and are even aggravated after the rigor has passed and the febrile stage is fully developed; in the mean time, the *face* becomes flushed, and sometimes deep red and swollen in appearance; the *eyes* are shining and suffused; the conjunctivæ more or less hyperæmic and often deeply injected, in severe cases

presenting a fiery, inflamed appearance which is accompanied by photophobia; the *skin* becomes hot and dry, and there is apt to be,



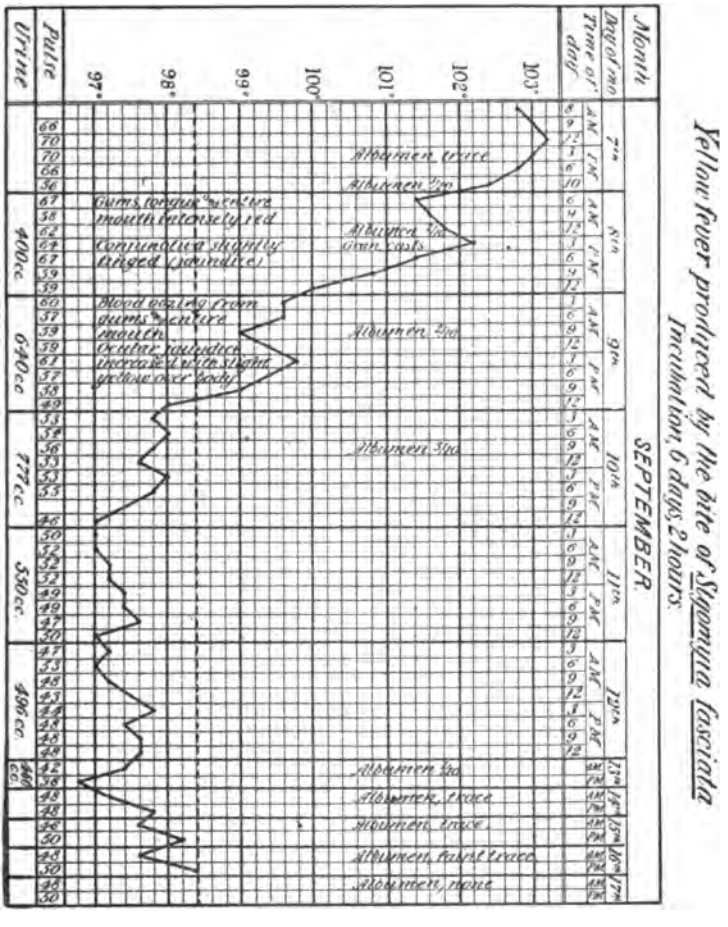
especially in patients of a nervous temperament, great *restlessness* with *jactitation.*

It is evident, from the account given of the symptoms manifested at the outset of an attack, that these are not sufficiently characteristic to determine the nature of the disease, and in the absence of a prevailing epidemic its early recognition will depend largely upon other



facts relating to the antecedents of the patient, etc. The complete clinical history of a case, however, gives a tableau which is easily recognized by one who is familiar with the disease. In this clinical history the thermometric observations form a very important item.

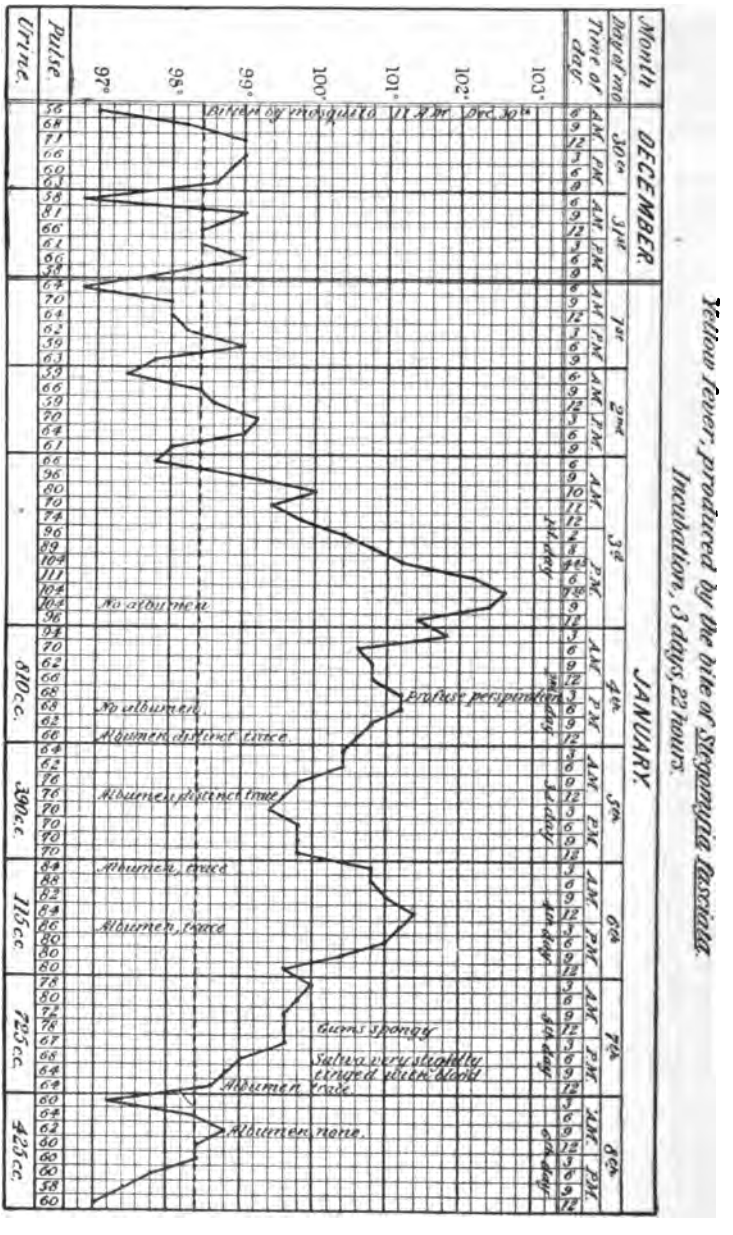
Yellow fever is a disease of a single febrile paroxysm, lasting from forty-eight hours to seven or eight days—more commonly from three to five days. The acme of temperature is reached at the outset, and from this time the temperature line is a descending one, interrupted sometimes by a slight evening exacerbation, up to the termination of the first period of the disease—*febrile stage.* The second stage is characterized by great prostration of the vital powers, and lasts from a



few hours to two or three days—*stage of calm;* the temperature during this stage sometimes remains a degree or more above the normal, but more commonly it is normal, or even subnormal for a time. This is followed in severe cases by a *reactionary fever* of irregular duration which presents a more or less remittent character.

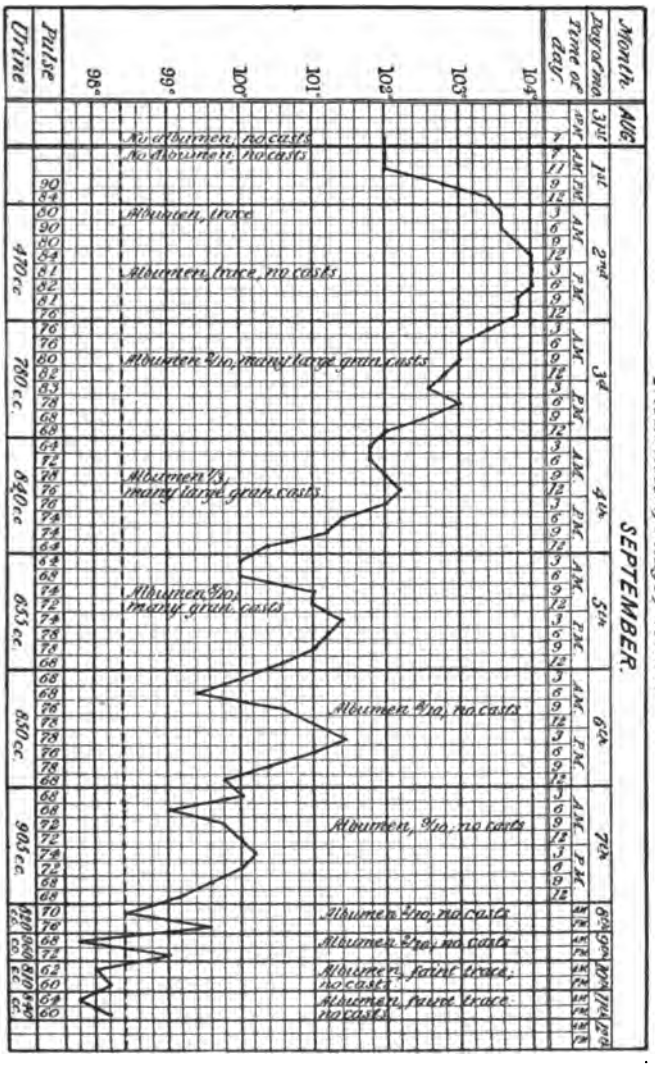
Naturally the typical temperature curve is disturbed by complications—visceral congestions, abscesses, parotitis, etc. It is also dis-

turbed by indiscretions in diet, over-active medication, and by moral causes (especially fright and grief). In mild cases the acme of tem-



perature is reached during the first two or three hours of the attack. In more protracted and severe cases it is not reached until the second or third day, rarely later. In an analysis of 192 cases recorded by

Faget, Jones, and myself, the acme was reached on the first day in 102, on the second in 54, on the third in 33, and on the fourth in 3. The temperature rarely, if ever, exceeds 108°. The highest temperature recorded by Faget was 107.2°. Thornton, in a total of 143 cases occurring at Memphis, noted a temperature of 108° in a single in-


Yellow fever, produced by the bite of Stegomyia fasciata.
Incubation, 3 days, 7 hours.
SEPTEMBER.
Albumen, trace.
Albumen, trace, no casts.
Albumen 1/10, many large gran casts.
Albumen 1/5, many large gran casts.
Albumen 1/20, many gran casts.
Albumen 1/10, no casts.
Albumen, 1/10, no casts.
Albumen 1/10, no casts.
Albumen 1/10, no casts.
Albumen, faint trace, no casts.
Albumen, faint trace, no casts.

stance. With this exception, 106.5° is the highest temperature recorded by him. In my own observations 106° has been the highest temperature noted. The temperature often rises rapidly just before death, and a very high post-mortem temperature (108° to 110°) is a common phenomenon.

The temperature charts published in connection with this article were made by members of the board of which Major Walter Reed, Surgeon, U. S. A., was president, and represent cases of yellow fever resulting from inoculation by infected mosquitos and by injection of blood of yellow-fever cases. Experts will at once recognize these as typical cases of yellow fever, such as are seen in every epidemic.

In certain cases the initial paroxysm is divided, by a more or less complete remission, into two or more distinct periods of from two to four days' duration. These cases are not sufficiently numerous to require a modification of the general statement that yellow fever is a continued fever of a single paroxysm. In relapses, which may occur from imprudence at any time after the termination of the first febrile paroxysm, the characters of the initial paroxysms are repeated, but in non-fatal cases the duration is usually not so long.

The *pulse* in sthenic cases is full, strong, and hard at the outset of the attack, and may reach 120 or more pulsations in the minute, more commonly not more than 100 to 110. It diminishes in rapidity and force as the disease progresses, and this occurs even when the febrile heat is not reduced for two or three days, and is considered by Faget a valuable diagnostic sign. During the second stage of the disease, the pulse, however hard and accelerated it may previously have been, becomes preternaturally slow and soft. The feebleness of the heart, which has undergone a certain degree of fatty degeneration, is shown by this very compressible and slow pulse, which is often reduced to forty, and sometimes even to thirty, beats per minute. This constitutes a very characteristic feature of the disease, and affords an important indication for treatment during the period of depression, or "calm."

The *tongue* is sometimes but slightly coated at the outset, and is usually moist; generally it quickly becomes covered with a white coating, which may be in streaks; the margins as a rule remain red; very commonly the tongue is narrow and pointed, differing in this respect from the broad, flabby tongue of the malarial fevers. In the progress of the disease it often becomes dry, and the coating assumes a brownish color, or it may become very foul and loaded with sordes.

The *face* is at first flushed or bright red and swollen, or it may be of a dusky violet hue; this, with the deep red suffusion of the eyes in severe cases, is quite characteristic. The countenance often has an expression of anxiety or pain, or of dejection; again it may appear dull and indifferent.

In the last period of the disease, in fatal cases, the features become shrunken—sometimes bloated and flabby—the brows are often contracted, and the eyes sunken, with ecchymosed lids.

The hyperæmia of the conjunctivæ in mild cases may be temporary,

in the more severe ones it is apt to last through the first period, and in quickly fatal cases the eyes may be deeply injected throughout. Usually by the third day a careful inspection will show that the conjunctivæ have a yellowish tinge which becomes more intense as the disease progresses.

The *skin* is hot and dry in some cases throughout the first period; in others it soon becomes moist and there is a tendency to free perspiration, which is readily induced by covering with blankets, warm drinks, etc. Even in those cares in which the skin is hot and dry, the termination of the first period is marked by a soft, cool, and usually moist surface. In exceptional cases the skin remains hot and dry up to the fatal termination. When death occurs in the stage of depression, the surface becomes cold and often is covered with a clammy sweat. Many authors have spoken of a peculiar odor given off from the surface of yellow-fever patients, and various attempts have been made to define its character by comparison with other known odors. Dr. Rush said that it resembled that of "the washings of a gun." Dr. Jackson describes it as "sickly and faint, and not unlike the smell of a fish-market."

The color of the skin, which has given name to the disease, is not always seen, but usually a yellow discoloration begins to make its appearance toward the end of the first period, and later becomes more intense, lasting for some time after convalescence is established. It varies much in intensity from a slight yellow tinge to a deep orange or saffron color. In certain cases the skin presents a mahogany color or that of bronze. In fatal cases the yellow color is developed immediately after death, even if it has not been very noticeable before dissolution took place.

The proportion of cases in which this yellow color of the skin is observed varies greatly in different epidemics, and even in different periods of the same epidemic. Dr. Rochoux states that in the West Indies it is absent in about half of the cases that recover. Bérenger-Féraud, referring to this statement, says that there are in fact two kinds of icterus in yellow fever, the one due to blood pigment, the other to bile pigments. The first is considered by Féraud to be constant and characteristic; it occurs at a time when the urine is albuminous and free from bile, and manifests itself about the beginning of the second stage by a yellow tinge of the conjunctivæ, of the face, and of the skin over the great vessels. It coincides with the period during which the hemorrhagic tendency of the disease manifests itself. The other form of icterus appears at the end of the second period, or during convalescence, at a time when the urine contains a notable quantity of bile pigments; it gives rise to the deep orange or saffron color of the skin which is so striking, but which occurs only in a certain

proportion of the cases, and cannot be considered an essential character of the disease. We are disposed to think that Féraud is quite right in this account of the icterus of yellow fever. A slight yellow discoloration of the conjunctivæ can commonly be detected during the second stage, even in mild cases in which no discoloration of the skin is perceptible.

Various skin eruptions have been described as occurring occasionally, but there is nothing characteristic about any one of them unless it is the erythematous eruption about the scrotum which Bérenger-Féraud believes to be pathognomonic of the disease. Other eruptions mentioned as occurring occasionally are petechiæ, vesicular and pustular eruptions, livid spots and vibices, erythematous patches about the knees and elbows, or a general erythematous eruption, papular eruptions, pustules about the mouth, furuncles, etc.

The *urine* in yellow fever, even during the first period, is reduced in amount below the normal standard. This marked reduction, and in fatal cases very commonly complete suppression, is a notable feature of the disease.

The presence of albumin in greater or less amount is a symptom which is so constant that it has come to be generally accepted as one of the pathognomonic features of the disease.

The diminution in the amount of urinary secretion in connection with the amount of albumin present is of importance in a prognostic sense, as it is to a certain extent an index of the gravity of the attack.

The most marked diminution occurs during the stage of depression, and the few ounces secreted in the twenty-four hours, in severe cases, are loaded with albumin to such an extent as to form coagula which occupy one-half to two-thirds of the contents of the test-tube.

In mild cases only a slight trace of *albumin* may be found in the urine for a day or two, but usually the deposit is sufficiently abundant after the second day to leave no doubt as to its character; it becomes more abundant at the termination of the first stage, and in severe cases throughout the stage of calm, at which time suppression is very liable to occur, especially if, as a result of exposure, the cutaneous transpiration is checked. The early appearance and abundant presence of albumin is generally recognized as an evil prognostic. The reappearance of albumin, after it has once disappeared, indicates a relapse.

The amount of *urea* eliminated by the kidneys is less than normal, and in inverse proportion to the severity of the attack. According to Cunisset, the quantity is generally in proportion to the amount of urine secreted, and when the amount increases it is a favorable symptom. Uric acid is also said by this author to be present in diminished quantity, but in much less proportion than the urea. He says: "We

have seen urine, containing only 7 gm. of urea per litre, give a relatively abundant deposit of uric acid." Bile pigments usually appear in the last days of sickness, and their presence is generally considered a favorable prognostic sign. In exceptional cases the urine may contain blood, from renal or vesical hemorrhage. The urine in yellow fever almost invariably presents a decidedly acid reaction.

The symptoms connected with the *nervous system* are varied. In mild cases the intellect remains undisturbed, and only a moderate amount of transient pain in the head and back marks the onset of the attack. In severe cases the frontal headache and rachialgia are most distressing, and may last throughout the first period of the disease. This stage is also one of great restlessness and jactitation; the patient sleeps but little, and his sleep is apt to be disturbed by distressing dreams; the mind often seems to be in a state of tension, the patient is watchful, excited, and anxious. In other cases the mind is calm, and in others again there is a condition of apparent apathy or indifference. Delirium is not a very common symptom in yellow fever, and the intellect often remains unclouded throughout, even in fatal cases. Some cases, however, are attended with incoherency of ideas, or hallucinations, and in some there is active delirium. More frequently the mind falls into a torpid condition, the patient is somnolent, and, when awakened, is disposed to be taciturn. A certain number of fatal cases are characterized by active delirium, followed by coma, and a greater number by coma gradually developed. In a limited number of cases death is preceded by convulsions, and occasionally tetanic symptoms of more or less general character have been noted. Among the nervous symptoms may be mentioned deep sighing respiration, sometimes of a spasmodic character. Naturally the *respiration* is increased in frequency during the febrile stage; in the stage of calm it again becomes normal in mild cases, or sighing and spasmodic in those of a graver character.

There is complete *anorexia* during the first stage of the disease, but when the remission occurs patients are very likely to desire food, and even to insist upon having it. *Thirst* is a constant symptom during the febrile stage, and also in the second period, especially when there is frequent and copious vomiting—black vomit. The *bowels* are commonly somewhat constipated at the outset. In the second period of the disease there is apt to be more or less diarrhœa, and in fatal cases a dark fluid is often discharged from the bowels, resembling precisely that from the stomach. Occasionally there is a discharge of pure blood, the result of intestinal hemorrhage. A choleraic form of the disease is sometimes met with, in which we find profuse diarrhœa and collapse, similar to that in the algid stage of Asiatic cholera.

Symptoms connected with the *stomach* form a prominent part of

the clinical history of yellow fever. The characteristic *black vomit* which has so much occupied the attention of medical authors, is for the vulgar the most striking feature of the disease, and even many physicians reserve their diagnosis in early cases during an epidemic until they have had ocular evidence that the vomited matter is black. The common name of the disease in Spanish countries—*vomito negro*—refers to this symptom. Yet in a majority of the cases there is no vomiting of black matter. Indeed, this is recognized as a very grave symptom, and although a considerable number of recoveries occur after the characteristic black vomit has been ejected, this may be considered an exception to the general rule.

Vomiting is a common symptom during the first period of the disease; sometimes the fluid ejected has a yellow color from the presence of bile, but more frequently it is colorless and consists only of the fluids ingested, containing, in suspension, a little mucus from the stomach; it is almost always acid. In favorable cases vomiting ceases with the first period of the disease; in those of a graver character, after an interval, perhaps, of twenty-four hours or more, during which there is more or less gastric distress, or a feeling of weight and discomfort, vomiting again occurs, either of a clear acid fluid, or of one of the varieties of black vomit. At first the black material may be in the form of little flocculi suspended in a transparent fluid—"coffee-ground vomit," and as the case progresses the amount of this material increases until the whole fluid appears to be uniformly black. Upon allowing it to stand, however, it commonly separates into two portions, and it will be seen that it still consists of a clear liquid with the black matter in suspension. Upon microscopic examination it will be found that the colored material is made up of little masses which are not black, but have a yellowish-brown color. A careful examination of recent specimens shows that these little masses contain decolorized and more or less deformed red blood corpuscles, and granular leucocytes, and that the brown matter is diffused about these agglomerated cellular elements, and the matrix of mucus in which they often seem to be included. There is no doubt that the black vomit is due to passive hemorrhage from the gastric mucous membrane, although this has been disputed by some authors—Freire, Carmona, Gibier. Formerly it was maintained by some that the black matter was a secretion from the stomach, and by others that it was "vitiated black bile." I have myself repeatedly verified the fact by microscopic examination that it contains the cellular elements of the blood. In certain cases there is vomiting of pure blood, resulting from more active gastric hemorrhage. The black vomit is not always discharged during life, but it is extremely rare not to find it in the stomach after death.

The fact that the gastric mucous membrane is seriously involved

in this disease is shown not alone by the vomiting, the passive hemorrhage, and the post-mortem appearances, but also by the constant feeling of discomfort or pain in severe cases, and by a marked tenderness upon pressure over the epigastrium.

Hemorrhage may occur not only from the mucous membrane of the stomach and intestine, but also from that of the mouth, nose, bladder, and uterus, and even from the eyes or ears. In some epidemics epistaxis is quite common; it may occur during the first period of the disease, but is more frequent during the second, at which time the general tendency to hemorrhage is developed. Next to epistaxis, hemorrhage from the buccal mucous membrane, and especially from the tongue, the gums, and the lips, is the most frequent.

In mild cases of yellow fever, *convalescence* is quickly established. Instead of the usual depression which marks the second stage of the disease, the patient, after a fever of three to five days' duration, may enter almost immediately into convalescence, and within a week may be ready to resume his usual avocations. But in severe cases convalescence is often slow and may be interrupted by various *complications* —parotitis, buboes, furuncles, abscesses, hepatitis, diarrhœa. In the army, experience shows that but few of those attacked are able to resume their duties in less than ten days, and a considerable number remain in hospital from thirty to fifty days. Blair found the average number of days during which patients were retained in hospital after convalescence was established to be 6.55 for mild cases, and 7.91 for grave cases.

Relapses occur for the most part during the early period of convalescence, or before it is fairly established; they are generally regarded as even more dangerous than the first attack. Occasionally a relapse, or second attack, occurs as late as from two to four weeks after the termination of the febrile period of the first attack.

Prognosis.

The prognosis in yellow fever should always be guarded, for not only is it a very fatal disease in its severer forms, but cases which appear mild at the outset may suddenly assume a grave character. It is more favorable in the case of women and children than in men, and is especially unfavorable in those of intemperate habits, and in plethoric persons who have recently arrived in the infected locality. The principal guide in forming a prognosis at the outset of a case is furnished by the temperature observations. When the body heat does not go above 103° to 103.5° F. during the first two days a favorable result may be anticipated. Later, the amount and character of the urinary secretion is the most important prognostic indication. When

this is scanty and heavily loaded with albumin, the case is very grave although the general appearance of the patient may be favorable, and he may insist that he is "all right" and wants something to eat. On the other hand, hopes of a favorable issue may be entertained even in cases characterized by great prostration, and in which the hemorrhagic tendency is pronounced, if the urinary secretion is tolerably abundant and the quantity of albumin small. The throwing up of black vomit is by no means a fatal sign, but as a rule the passive hemorrhages which occur during the second stage of the disease are of grave import. Epistaxis occurring during the first stage has been considered by some authors a favorable event (?).

The early appearance of jaundice is an unfavorable sign; as are also frequent vomiting and great distress and tenderness in the epigastric region. Intense and long-continued injection of the conjunctivæ, giving the eyes a fiery-red color, is unfavorable. Delirium, great restlessness and jactitation, and sighing respiration are all symptoms which give reason for anxiety as to the result.

The prognostic indications as furnished by temperature observations are shown in the following table, made by the writer, some years since, from a series of cases in which a complete and careful record had been made:

Cases in which the temperature was—	Number of cases.	Number of deaths.	Percentage of deaths to cases.
107° F. and above.....	13	13	100
106° to 107° F	9	9	100
105 " 106	36	22	61
104 " 105	80	24	30
103 " 104	87	6	7 nearly.
102 " 103	29	0	....
101 " 102	15	0	....
Total	269	74	27.5

Mortality.—The mortality from yellow fever varies greatly in different epidemics and among different classes of the community.

Among the natives of cities in which the disease is endemic, or in which it has frequently prevailed as an epidemic, it may be as low as from seven to ten per cent. One reason for this comparatively small mortality is found in the fact that a considerable proportion of the cases in such a community are among children. Among unacclimated adults, the mortality ranges from twenty to sixty per cent., and under certain circumstances even exceeds the latter figure. In the great Philadelphia epidemics of the eighteenth and the beginning of the nineteenth century, the mortality was from twenty to eighty per cent. In the French Antilles, according to Dutrouleau, the mortality during the years 1851 to 1857, inclusive, ranged from 12.9 per cent. to 50 per

cent. Blair gives the mortality at the Seaman's Hospital at Georgetown (Demerara) in 1838 as 19.5 per cent.

At Vera Cruz the mortality for seven years (1875–81), according to Dr. Molina's statistics, was 41.78 per cent. in the hospital for men, and 41 per cent. in the hospital for women. In Rio Janeiro the mortality for the year 1870 was 17.4 per cent. In the epidemic of 1873 it was 23.3 per cent.

Dr. Bemiss gives the mortality rate for the city of New Orleans during the great epidemic of 1878 as 16.66.

Diagnosis.

Notwithstanding the well-marked features of a typical case of yellow fever, it very often happens that the early cases in an epidemic are not recognized, and even in fatal cases, with the assistance of an autopsy, physicians not previously familiar with the disease often differ as to the diagnosis. At the outset of an attack, indeed, there is nothing sufficiently characteristic in the symptoms to enable even an expert to decide definitely that the case is one of yellow fever, although there are certain indications which may give him a strong suspicion that it is.

The occurrence, in a Southern seaport, of a group of cases of ephemeral fever, in a particular locality, especially among the colored population, should always arouse suspicion and lead to investigation. When in such a city, or in any place within the limits of yellow-fever invasion, and during the summer months, we hear that a "malignant form of malarial fever" has appeared in a certain limited area, a single house or square or district, we shall not be apt to go wrong in the inference that the disease is yellow fever. Malignant forms of malarial fever belong to the country rather than to the city, and cases do not occur in groups within city limits, where the malarial poison is not generated in its most intense form, if at all. Formerly, very much uncertainty as to diagnosis arose from mistaken ideas as to the etiology of the disease. A considerable number of physicians in the United States maintained that yellow fever and the malarial fevers are closely allied, if not identical, diseases, due to the same general causes, and the idea was very prevalent that, under the influence of meteorological conditions, a mild form of malarial fever might be transformed into the malignant yellow fever. Under this idea physicians felt justified in calling the mild cases in an epidemic malarial fever, and in reserving the name yellow fever for those in which a yellow skin, highly albuminous urine, and black vomit make up the clinical tableau to which they gave the name yellow fever. Of these three prominent features only one is a constant character which can

serve in establishing the diagnosis in mild cases. This is the presence of *albumin* in the urine. At some period of the disease, even in the mildest cases, there will be a distinct trace of albumin in the urine, as shown by the usual tests, and this will generally be sufficiently abundant to leave no doubt in the mind of the observer as to the nature of the precipitate. In 61 cases occurring during an epidemic in Jamaica, Donnet found albumin present for the first time: in 2 cases on the first day; in 11 cases on the second day; in 19 cases on the third day; in 14 cases on the fourth day; in 6 cases on the fifth day; in 4 cases on the sixth day; in 4 cases on the seventh day; in 1 case on the eighth day. It will be seen that, in by far the larger number of cases, the presence of albumin was verified on the second, third, or fourth day. The value of this test in the differential diagnosis of yellow fever is indisputable. It is true that a trace of albumin is sometimes found in the urine in severe fevers of malarial origin, but in cases of yellow fever of equal severity, as compared with these, the precipitate would, as a rule, be very abundant on the third or fourth day of sickness, forming a deposit to the extent of one-fourth to one-half the contents of the test-tube, or even more. At the same time a microscopical examination would show the presence of numerous granular casts from the tubuli uriniferi. These are found also, although in a smaller number, in the urine of the milder cases during the second stage of the disease. For diagnostic purposes the character of the febrile paroxysm, and especially the phenomena following this which mark the second stage of the disease, are the most important. It must be remembered, however, that while the stage of depression is commonly marked by a normal, or even subnormal, temperature, in a considerable number of severe and fatal cases the temperature still remains a degree or two above the normal when the cool skin and slow, soft pulse would indicate, if the thermometer were not used, that there was complete apyrexia; or again the skin remains dry, and the patient falls into a typhoid condition, with a fluctuating temperature, without having had a complete remission of febrile heat.

The second stage of the disease is, however, commonly well marked in non-fatal cases, and is its most characteristic feature; the remarkably slow and soft pulse; the evident prostration of the vital powers, although the patient may be comfortable, and even cheerful, and desirous of getting up, or of taking food; the yellow tinge of the conjunctivæ and skin—not always present; the tenderness on pressure in the epigastric region, and often a feeling of weight and distress in this region, attended with intense thirst and vomiting of a transparent acid fluid, or of the characteristic black vomit; the tendency to passive hemorrhage from the mucous surfaces of the mouth or nose; oozing of dark blood from the gums, or lips, or sides of the red and fissured tongue;

the scanty urinary secretion and the presence of albumin, usually in considerable amount; all of these symptoms constitute an *ensemble* that for the practised eye and hand is unmistakable.

Pathological Anatomy and Histology.

The exterior of the body of an individual who has recently succumbed to yellow fever presents an appearance which is quite characteristic. The icteric color of the skin, although often not noticeable during the last hours of life, is developed in a large majority of the cases very soon after death. The color is that which is seen to follow a bruise in which there has been an effusion of blood, and the origin of the pigment is no doubt the same. The icterus from bile pigments, which occurs not infrequently during convalescence, and which may be seen in cases fatal in a relapse or at a late period of the disease, gives a uniform saffron-yellow color to the surface of the body and conjunctivæ. In the icteric discoloration of which we speak at present the color is not so intense and not so uniformly distributed. The depending portions of the body, and especially those subjected to pressure, have a deeper coloration, and are more or less livid and mottled from hypostatic congestion. Dutrouleau has shown, by placing the body upon the abdomen or side that this ecchymotic appearance of the back is due to position and pressure. In this case it is still the most dependent part which shows the livid marbled appearance referred to. The face and hands frequently appear cyanosed, or the face may be livid and turgescent like that of one recently drowned. A little stream of black vomit is frequently seen trickling down from the corners of the mouth, or a similar fluid may escape from the nostrils, and the lips and gums may be soiled with dark blood which has oozed from them.

Cadaveric rigidity is quickly established and well marked.

The appearances observed upon removing the calvarium are usually those of hyperæmia of the *brain* and its *meninges*. The pia mater is almost always congested, and the vessels of the brain are abnormally full of blood; the pons and medulla are especially in a condition of hyperæmia. There is more or less effusion into the subarachnoid space and in the ventricles; this is sometimes turbid and has a yellow color. The surface of the brain presents sometimes little hemorrhagic points, and its substance, like the tissues of the body generally, has a more or less pronounced yellow tinge.

Usually the *lungs* present no evidence of pathological changes; occasionally they are congested and contain hemorrhagic infarctions.

The fluid in the *pericardium* is often increased in amount and has a yellow color; in rare cases it contains blood. The heart is commonly

paler than normal and, according to some authors, is often soft and friable owing to fatty degeneration of its muscular tissue (Riddel, Schmidt). This is denied by others (Crevaux, Guitéras, Gamo Lobo). Woodward, who examined the material brought back by the Havana Commission of 1879, agrees with Guitéras that his sections did not present any decided evidence of fatty degeneration, but remarks: "This by no means proves that it does not occur in certain cases, perhaps in certain groups of cases."

Several of the most competent observers agree that there is a fatty degeneration of the walls of the small *blood-vessels* and *capillaries* of the various organs, and account in this way for the hemorrhagic tendency of the disease. This is certainly a more rational explanation than the one so frequently offered, viz., that the hemorrhages are due to the disorganized and diffluent condition of the blood. A moment's reflection should show that this explanation is insufficient, and that the blood, however diffluent, cannot escape so long as the vessels are intact. Ecchymotic points, or hemorrhagic infarctions, are sometimes found upon the surface or in the substance of the heart, as well as in other muscles of the body and the organs generally. The cavities of the right side of the heart usually contain soft coagula or dark-colored fluid blood, and the right ventricle sometimes contains a more or less decolorized fibrinous clot.

The *blood* in yellow fever has been described by many observers as "completely disorganized" as to its histological elements. This is a mistake as is shown by the numerous photo-micrographs made by the writer while in Havana, in 1879, from the blood of cases near a fatal termination. Both the red and the white corpuscles retain their normal appearance, and I have frequently seen the leucocytes undergoing their characteristic movements, even after twenty-four hours, in blood which had been preserved in culture cells. In the days of bleeding numerous observers mentioned the fact that the blood did not coagulate readily, or formed a soft, loose, coagulum from which the serum did not separate. The same is true of the blood in the heart and large vessels after death; it is fluid and dark colored. Although there is no general destruction of the red corpuscles, it is probable that a considerable number of these elements perish in severe cases, for the serum contains free hæmoglobin, which gives it a yellow color even as early as the third or fourth day. This yellow color is seen in the serum obtained and in blood drawn for microscopical examination. In blood obtained near the termination of a fatal case, and in post-mortem blood, this color is very pronounced, and increases in intensity by further solution of the hæmoglobin when the specimen is kept for a time; in the mean time the blood discs become paler than normal. In specimens kept in culture cells I have observed the formation of

beautiful crystals of hæmatoidin. This passing of the hæmoglobin into the serum, which is no doubt the cause of the yellow discoloration of the tissues in yellow fever, has been ascribed to the presence of bile. This view is not sustained by the chemical researches of Cunisset, a French author, who has arrived at the following conclusions:

"Yellow fever is not a poisoning by the bile; at the outset of the malady the biliary pigments are rarely found in the blood or in the urine. They appear generally only during the second period, and in a great number of cases they are not to be found at all.

"The biliary salts, of which the powerful action of 'deglobulization' admitted by certain authors might explain the disorders which the malady presents, do not exist either in the matters vomited, or in the urine, or in the blood, except, in certain cases, in very feeble quantity. In view of the profound alterations of the liver, this absence of the biliary salts is easily understood, and the defective depuration of the blood is to be looked upon as a complication rather than a determining cause of the malady."

The most important pathological changes in yellow fever are found in the organs contained in the cavity of the abdomen. The mucous membrane of the *stomach* is always found to be more or less hyperæmic; the congestion is commonly not general, but is confined to smaller or larger spots or districts, in which it is observed to proceed from one or more centres. From these centres it extends or radiates in a lesser degree, either gradually to be lost, or to pass over to another congested district. It is owing to this peculiarity of the congestion that it presents no uniformity of character, but is observed to spread irregularly over larger or smaller portions of the membrane (Schmidt). In addition to these congested patches there are often to be seen small red patches resembling ecchymoses, but which, according to Schmidt, consist of "an unbroken network of minute vessels congested with blood, and identical with that network of large capillaries which surrounds the aperture of the gastric glands." Crevaux believes that a fatty degeneration of the cells which line the gastric glands and the capillaries of the mucous membrane is the most important lesion here. Other authors speak of an acute gastric catarrh as the process indicated by the appearance and histological examination of the mucous membrane; others again deny that there is any inflammation. My own examination of thin sections stained in various ways shows that in a certain proportion of the cases there is evidence of inflammation, as shown by the presence of an unusual number of leucocytes in the submucous coat.

The small *intestine* commonly contains more or less black matter, either fluid and resembling that found in the stomach, or mixed with mucus and smeared over the mucous coating, especially in the ileum.

This no doubt comes partly from the stomach, but in other cases is due to passive hemorrhage from the mucous membrane of the intestine itself. This membrane presents arborescent patches of congestion, or portions of the canal may be uniformly red from hyperæmia of the mucous coat; the color varies from pale red to a reddish-brown, and is usually more marked in the lower portion of the ileum than elsewhere. The large intestine occasionally presents similar arborescent patches of congestion, but usually it has a normal appearance.

The appearance of the *liver* in yellow fever is characteristic, at least so far as acute febrile diseases are concerned. Usually it contains less blood than in the normal condition, and is of a pale yellow or brownish-yellow color, similar to that of new leather in its various shades; occasionally it is gorged with blood, and livid, deep blue, or dark purple in color. In the victims of chronic alcoholism, it often presents the nutmeg appearance of cirrhosis. The dimensions do not differ materially from the normal, but the consistence is modified by the fatty change, which gives the characteristic color, and the parenchyma is easily torn and is more or less friable. On section it is found to be dryer than in the normal state, except in the comparatively few cases in which it is hyperæmic; these are, as a rule, cases which have proved fatal at a very early period—a fact which indicates that there is a stage of congestion antedating that of anæmia and fatty degeneration. According to Crevaux, this congestion is located especially in the portal radicles surrounding the lobules, and is attended with œdema of the interlobular connective tissue. Whether this primary congestion is a constant phenomenon or not, it is certain that in a majority of the autopsies the liver is found to be anæmic and to present more or less evidence of fatty change in the hepatic cells. This is not, however, a uniform process, but areas of greater or less extent are seen, in which the cells are infiltrated with fat globules, while in other places the cells appear normal. The fatty cells contain one or several fat globules of varying dimensions, and the protoplasm is reduced in quantity according to the extent of this fatty change. The nuclei very often remain intact in the cells infiltrated with fat, but according to Schmidt "a great number of the nuclei also undergo fatty degeneration." Often a collar of normal cells remains about the central vein, while those cells nearer the periphery of the lobule contain numerous fat globules.

The *kidneys* are also the seat of important pathological changes in the disease under consideration. This consists essentially in a parenchymatous nephritis. Externally no material change is noted in the organs. They do not vary greatly from the normal size, and usually are normal in appearance. When the attack has been brief, however, they may be hyperæmic and of a deep red color. Crevaux believes

that the changes found in the parenchyma of the organ are usually preceded by a stage of congestion; Schmidt agrees with him, and states that he has met with a limited number of cases in which death had occurred during this stage of hyperæmia. Ecchymosed spots and hemorrhagic foci are frequently seen beneath the capsule or in the cortical substance. In the latter situation little globular hemorrhagic points, the size of a pin's head, have been observed, which upon examination proved to be the distended capsules of the glomeruli. The change in the renal epithelium consists in a cloudy swelling, followed by fatty degeneration and desquamation. Every grade of change may be seen in the same section, from a slight degree of cloudy swelling to complete disorganization and desquamation of the cells. Whole bundles of tubes may often be seen which have been stripped of their epithelium and are entirely empty. In thin sections the lumen of the tubules is seen in places to be filled with infarctions of various appearance. Some are homogeneous and translucent, and it may be more or less colored with blood pigment; these are composed of an albuminous material. Other infarctions are formed of the granular débris of the renal epithelium; or we may have a mixture of the granular and albuminous material, in which case the latter forms a matrix in which the granules are embedded. These infarctions correspond with the casts found in the urine; those of a granular character are most abundant, and in them the granules often have a fatty appearance. There are also accumulations which differ from these in the fact that they are deeply stained by the aniline colors. They seem to be made up of the nuclei of the cells, sometimes intact, although swollen and compressed; more commonly massed together, or broken into irregular fragments. At least this seems to me to be the most probable interpretation of those infarctions which are stained by nuclear staining agents.

The *suprarenal bodies*, according to Schmidt, undergo pathological changes similar to those observed in other organs, "consisting in the infiltration of fat and hæmoglobin, derived from the blood, and preceded by hyperæmia of the organ. The infiltration or extravasation of hæmoglobin absorbed by the cells is greater and more general here than has been observed in any other organ. Almost in every case examined it involved the whole medullary substance, from which it extended into the inner and middle layer, sometimes even into portions of the outer layer of the cortical substance. The degree of this pigmented infiltration is sufficiently great to be always distinguished by its brown color in sections of fresh specimens; in some cases, even, it appears dark brown.

The *spleen* does not undergo any marked alteration in yellow fever.

Treatment.

The unsatisfactory results obtained in the various methods of treatment proposed are shown by the fact that a majority of the physicians in those parts of the world where yellow fever prevails, who have had an extended experience, agree that active medication is injurious, and have settled upon an expectant or symptomatic treatment, with careful nursing, as giving the most favorable results. Yet the records of the past show that a certain proportion of the cases recover under all modes of treatment, even the most active and opposed to our present views. The famous Dr. Rush, of Philadelphia, was thoroughly convinced of the advantages of copious bleeding during the first stage of the disease, and ascribed the more favorable results obtained in the epidemic of 1793, as compared with those of 1741, 1747, and 1762, to the more liberal use of the lancet. Venesection was often repeated from five to ten times by Rush and other practitioners of his date, and the amount of blood extracted often exceeded one hundred ounces—one hundred and fifty and even two hundred ounces in some cases. This excessive bleeding was soon abandoned, but the propriety of drawing blood at the outset of the attack was maintained by many practitioners in the United States and the West Indies for years after the "heroic" treatment of Rush had been abandoned.

Emetics were formerly considered an essential part of the antiphlogistic treatment. We speak of them only to condemn them, except in those cases in which at the outset of an attack there is evidence that the stomach contains undigested and fermenting material which is the cause of nausea and distress. In this case a simple emetic may be administered, with the sole object of unloading the stomach.

Purgatives have at all times been considered useful at the outset of an attack of yellow fever, and it is the standard treatment, wherever the disease prevails, to administer a cathartic of some kind as soon as the patient comes under observation. Opinions differ as to the best form of cathartic medicine; some prefer a mercurial, some a saline, and others a full dose of oleum ricini. On account of its prompt and thorough action and the absence of irritating properties, the last-mentioned medicine is a favorite in our Southern cities, in the West Indies, and in Brazil, especially in domestic practice among the creole population. The dose usually given might seem excessive to those who have not seen its favorable action; half a tumblerful, or even more, is the common dose for an adult—two to four fluidounces. Many physicians still prefer a mercurial purge, followed, if necessary, by a saline cathartic, and calomel is the mercurial usually selected.

The prevailing opinion that yellow fever is closely allied to the

malarial fevers led many physicians, during the first half of the last century, to prescribe *quinine* in the expectation that it might prove a specific in this disease. This expectation was not fulfilled, but there are still a certain number of experienced physicians who think a full dose at the outset of an attack to be beneficial; others consider it injurious, and as a rule it has been abandoned. In some of the new antipyretics and nervous sedatives we have agents which are probably superior to quinine for reducing the temperature and relieving the nervous symptoms; favorable reports have already been made with reference to some of these. In the epidemic of 1887 at Key West, Drs. Porter and Schweringen used *antipyrin*, as they believe to the advantage of their patients; it has also been prescribed quite extensively in Havana; but I have seen no exact statements as to the results obtained.

Many of the French physicians administer *bromide of potassium* as a nervous sedative, but we anticipate that antipyrin, or one of the more recent remedies of this class, will be found more useful in meeting this indication and for the reduction of temperature; there is no reason to expect, however, that they will prove to be specifics—they simply meet certain indications in the symptomatic treatment of the disease. Some of the physicians in Rio Janeiro have prescribed *jaborandi*, and think well of it, without, however, claiming that it has any specific power. When the skin is hot and dry it may serve a useful purpose, but it will be necessary to guard against the depressing effects of the remedy. Dr. Hebersmith, of the Marine Hospital Service, has given the *muriate of pilocarpine* in several cases, and he thinks with good results. Doses of gr. $\frac{1}{8}$ to $\frac{1}{4}$ were given hypodermically, and produced profuse perspiration, with reduction of temperature. But as several of his cases were in colored persons, and the initial temperature was moderate in all, we are not prepared to admit that recovery was due to the administration of this medicine.

Aconite, *digitalis*, and *veratrine* have been tested in the West Indies and elsewhere in full sedative doses. Féraud says of these medicines that "the attempts, although sufficiently numerous, have not yet furnished any decided results." After a careful trial of digitalis in doses of 2 to 3 gm. (ℳ xxx.–xlv.) of the tincture per diem, the author quoted arrives at the conclusion that in mild cases it seems to cause the fever to fall more quickly, but in intense cases it had not the same power. His general conclusion is that aconite, digitalis, and veratrine are superior to quinine, and that in moderate doses they are useful in allaying nervous excitement, and in moderating to a slight extent the fever. The writer has been in the habit of giving small doses of aconite, in combination with a mild diaphoretic, during the febrile stage of yellow fever, and has thought that some benefit was

derived from the treatment, although it must be confessed that this has not been very marked.

Dr. Bemiss, of New Orleans, writes of this class of medicines as follows: "It is the practice of some physicians to attempt the reduction of fever by large injections of cold water, which are said to prove very efficient antipyretics. Aconite, veratrum, tartrate of antimony, and ipecac are frequently exhibited. A cautious use of one or the other of the first two on this list may prove beneficial, but their injudicious or careless exhibition may do irreparable harm. *We have seen digitalis produce unquestionably good effect in mitigating fever, and have often administered it in doses of gtt. xxx.–lx. of the tincture every third or fourth hour.* It is best to give it in solutions of acetate of ammonia or potash."

Dr. Porcher, of Charleston, gives the following mixture as a gentle diuretic and diaphoretic:

℞ Acetate of potassium..... ʒ i.
Citrate of potassium..... ʒ i.
Morphine..... gr. i.
Camphor water..... ʒ vi.

M. A dessertspoonful to be given every two or three hours as long as there is heat of skin.

Some formula of this kind, which has a gentle sedative and diaphoretic effect, is useful so long as it does not disturb the stomach. Many practitioners refrain from giving any medicine at all, but permit the patient to swallow bits of *ice*, or small quantities of *ice-cold water*, at frequent intervals. This we quite approve of, or *iced carbonic-acid water* may be given. Others again give *warm drinks* to promote perspiration. This is the standard "creole treatment" in New Orleans, and in many parts of the West Indies. As the mortality among this class is small, they are well satisfied with the results obtained, but many strangers who have received the creole treatment die in spite of the dose of castor-oil, the *hot pediluvia*, and the orange-leaf tea. This treatment with careful nursing is, however, infinitely superior to the active medication of the novice in the treatment of this treacherous disease, for it is very easy to kill yellow-fever patients.

Bicarbonate of sodium dissolved in ice-cold water given in the dose of gr. iii. to v. (200 to 300 mgm.) every hour has been found of use for the relief or prevention of vomiting, and also appears to have a favorable effect upon the urinary secretion.

Baths of all kinds—hot, cold, tepid, medicated—have been given in yellow fever, and the evidence is varied as to their utility. The most judicious and experienced practitioners are, however, in accord as to the danger of disturbing the patient to the extent demanded by frequent baths, and, as a rule, content themselves with *hot pediluvia*

at the outset of the attack, and with sponging the surface with cold water or evaporating lotions to reduce the temperature. Very hot or very cold baths are condemned by Féraud on the ground that they are likely, even in the first stage of the disease, to produce visceral congestions, to which there is a great tendency in this disease. In the Southern part of our own country, and in the West Indies, a *hot mustard foot-bath*, administered at the outset of the attack, is a standard method of treatment. The patient is wrapped in a blanket, and sits with his feet and legs immersed in a bucket of water as hot as he can bear, to which a liberal quantity of mustard has been added. This has a tendency to relieve cerebral congestion and headache, and often produces a free perspiration. It may be repeated several times during the first twenty-four hours. Cold applications to the head, and repeated sponging of the hands, arms, and chest with cold water, give comfort to the patient and are of decided benefit on account of their antipyretic effect. Some practitioners recommend the use of tepid water for sponging the surface; Féraud prefers a mixture of one part of aromatic alcohol with three parts of water; Dr. Peyre Porcher recommends "the assiduous and protracted application of ice-cold water to the head, hands, and arms, as long as they are abnormally hot." This practice is justified by the results of his treatment, and we think it entirely safe and extremely useful. The knowledge that exposure to cool currents of air, or removing the bed-covers at night when the weather has suddenly turned cold, is attended with the greatest danger, on account of the visceral congestions—especially of the kidneys—which result from such exposure, has led many physicians to refrain from making use of cold lotions to the surface. The same apprehension has also led to an excessive use of blankets, and the poor patient, who is burning up with fever, is sometimes smothered in blankets and carefully guarded, to prevent him from exposing hand or foot to the air.

Toward the end of the first stage, and throughout the second stage of the disease, this watchfulness to prevent exposure of the body to cool currents of air is very necessary; indeed, it is important at all times if the external temperature is low, and especially at night; but the object in view can be obtained without loading the patient with blankets. He should be lightly covered, but carefully guarded from exposure if the weather is cool. At the same time the body may be sponged under the blanket, and iced water applied to the head, face, hands, and arms during the febrile stage.

Bérenger-Féraud speaks highly of the use of *large enemata of cold water*, frequently repeated, as a means of reducing the temperature. He has made extensive use of this mode of treatment, and has never seen any evil results from it.

The use of *sinapisms* and *vesicants* to relieve visceral congestion by revulsion to the surface is approved by experienced physicians everywhere. We prefer sinapisms, and believe that, as a rule, they will accomplish all that can be expected from a blister. The feeling of weight, distress, or absolute pain in the epigastric region, attended with nausea, which is largely due to the hyperæmia of the gastric mucous membrane, is often notably relieved by the application of a sinapism to the epigastrium. The patient, who has been restless and uncomfortable, will sometimes quickly fall asleep after such an application. In the same way cerebral congestion and headache may be relieved by revulsives to the extremities, and lumbar pain by the application of a large sinapism to the loins.

The scanty urinary secretion, and often complete suppression, in yellow fever seems to call for the use of *diuretics*, but unfortunately experience teaches that the most reliable medicines of this class do but little good. The kidneys are best relieved by those means which promote perspiration, and by revulsives applied to the loins. Complete suppression is rarely, if ever, relieved by any plan of treatment. In cases with a hot, dry skin and scanty urinary secretion, with lumbar pain, indicating congestion of the kidneys, we should expect benefit from the hypodermic administration of the muriate of pilocarpine.

Stimulants are rarely required before the fourth or fifth day, and must be given at first cautiously and in small doses, so as not to disturb the stomach; later, however, they are often absolutely demanded to sustain the feeble heart. During the second stage of the disease, when the pulsations of the heart often do not exceed 40 or 50 to the minute, there is always a tendency to syncope; this is especially manifested during the night or toward morning, and many a patient whose condition seemed satisfactory at the evening visit has been found by his physician dead the next morning. This dangerous period may often be tided over by the use of stimulants. When the stomach is very irritable a little iced champagne will often answer better than anything else; but perhaps the best form of stimulant is good brandy, given in teaspoonful doses, at intervals of half an hour, more or less, according to circumstances. It should be given ice cold. Later, milk punch, English ale, or porter may be given in liberal quantities, especially to those who are in the habit of using spirits.

Blair, whose opinion in all that relates to this disease is worthy of attention, prefers hock to any other form of stimulant. He says: "Of all cordials the best is Rhenish wine. When of good quality it is retained when everything else is rejected, and it is universally liked by the patients. I have seen the most excellent effects from its use, and have often given it to the extent of two bottles in twenty-four

hours. I believe it has saved many lives, and know of no substitute for it."

Medicines administered by the stomach to control vomiting, as a rule, are worse than useless. Minute doses of morphine, administered hypodermically, are sometimes useful in checking gastric irritability, but this is a dangerous remedy in yellow fever, and only very small doses are tolerated. Blair has seen stupor, prostration, and complete narcotism follow the administration of one-tenth of a grain. On account of the danger attending its administration he thinks that it will be more judicious to place it in the *index expurgatorius* of yellow fever. Bemiss, whose opinion is of equal value, says: "Vomiting should be met with epispastics, blisters, ice, and small doses of opium, in combination with cherry-laurel water and sodæ bicarb." An effort should be made to arrest *hemorrhage* by the use of ergot, the beneficial effects of which are sometimes well marked. As it is not likely to be absorbed by the stomach, and may cause vomiting, it will be best to administer ergotin hypodermically.

During *convalescence* the sulphate of quinine, in moderate doses, or citrate of iron and quinine, or the standard preparations of iron and of strychnine, will often be useful as tonics; and ale or porter, or a sound wine, in moderate quantities, will be found beneficial.

The *alimentation* in this disease, as in the specific fevers generally, is a matter of prime importance. During the first period of the febrile stage no food is desired, nor is it required. It is best to give nothing in the way of food for the first three or four days of sickness; after this, if the stomach tolerates it, an ounce or two of iced milk, or of chicken broth may be given every two or three hours. If the stomach is very irritable a smaller quantity at shorter intervals may be given, and it will be best to give the milk in combination with lime water. If the stomach will not retain this, or if it gives distress, do not push it further, but support the strength by nutritious enemata. Even when the stomach is quiet and the patient craves food, it will be necessary to give only liquid nourishment for two or three days, and then to allow nothing but the simplest and most digestible forms of solid food; for there is always danger of a relapse from imprudence in diet, even in the mildest cases.

BACILLARY DYSENTERY.

BY

K. SHIGA,

TOKIO.

DYSENTERY has existed in all lands from the earliest ages. Hirsch has remarked that it has always been widely disseminated over the earth, that no inhabited regions have been free from its ravages. Ayres also says that wherever man is found, there some of the forms of dysentery will appear. We need not here enter into the history of this disease since the subject has been exhaustively considered by A. Sodré in Vol. XIV.

Classification of Dysentery.

Dysentery has been subdivided into types upon epidemiological, clinical, or pathologico-anatomical grounds. Davidson from an epidemiological standpoint divides it into epidemic, endemic, war, and famine varieties; and upon clinical grounds into acute, fibrinous or pseudo-diphtheritic, and chronic varieties. Virchow differentiates two forms, viz., catarrhal and diphtheritic. Councilman and Lafleur consider two forms, viz., diphtheritic and amœbic. Osler recognizes four varieties, viz., acute catarrhal, tropical or amœbic, endemic, and chronic. Manson regards two types, viz., catarrhal and ulcerative. Among others the classification of Wesener and Kartulis is well known, especially in Germany. They divide dysentery into three forms as follows: (1) Endemic or tropical dysentery which most frequently occurs in the tropics or subtropics and which is produced by the amœba. (2) Epidemic dysentery which predominates in the temperate zone and which may be either epidemic or pandemic and occur in connection with war or famine. (3) Sporadic dysentery which may be of chemical, mechanical, or rheumatic origin. It may be endozootic or arise without assignable cause.

Such different classifications must always be undesirable. A proper classification can be made only upon etiological grounds. Since Lösch

in 1875 first discovered amœbæ in dysenteric stools these microorganisms have been regarded as the cause of tropical dysentery by a large number of authors, such as Koch, Kartulis, Kruse, Pasquale, Hlava, and Councilman and Lafleur. Kartulis summarizes the pathogenesis of amœbic dysentery as follows: (1) The constant presence of the amœba in every case of typical endemic dysentery. (2) The presence of the amœba in the walls of dysenteric ulcers and its absence in all other intestinal ulcers. (3) The constant production of dysentery in cats by the introduction of dysenteric fæces containing amœbæ. (4) The constant production of dysentery in cats by the introduction of liver-abscess pus which contains amœbæ but no other microorganisms. (5) The negative result of the introduction of the other microorganisms found in dysenteric stools. (6) The inability to produce dysentery in cats by the introduction of various other amœbæ found in healthy men.

Celli and Fiocca among others have advanced the following points, as the results of their researches, in refutation of the amœbic origin of dysentery: (1) There are types of dysentery in which amœbæ are not found. (2) It is true that by the introduction of dysenteric stools or cultures which contain amœbæ and other bacteria an amœba-free dysentery can be produced in cats. Also dysentery can be produced in cats by the introduction of such stools or cultures, even when these are previously heated so as to destroy the amœbæ but not the other microorganisms. (3) The so-called specific amœba is widely diffused. In Egypt the amœba coli is very abundant. Here it is found with great frequency in the stools of dysenteric patients, but is also present in the intestines of healthy persons who have never had dysentery. (4) Other species of amœba are present in the intestines of dysenteric and non-dysenteric patients as well as in those of healthy individuals.

The first point of contention has been elucidated by Flexner and Strong, who have found that in the tropics amœbæ are present only in chronic and not in acute dysentery. In regard to the other differences, these are still open questions which must be more extensively studied in tropical countries. In five out of thirty-five cases of dysentery observed by me in Japan, and which have been reported in the *Centralblatt für Bakteriologie*, 1898, No. 22 ("Ueber den Dysenterie-Bacillus"), amœbæ were present which were to be classified as amœba coli and differentiated from the amœba dysenterica of Lösch. Although it is not absolutely certain, yet it may be regarded as extremely probable that the amœbæ of Lösch are the producers of a special form of dysentery.

Various authors have conceived that certain bacteria might be the cause of dysentery, and nearly all the microorganisms which are found in the intestinal canal have been at times regarded as such excitants:

viz., B. coli, B. proteus, B. pyocyaneus, staphylococci, streptococci, diplococci, etc. Such conceptions have, however, remained unproven. In their endeavors to ascertain the chief causative factor of dysentery all observers have resorted to animal experimentation. It is true, however, that in all the animals hitherto used for this purpose no characteristic dysenteric lesions have been produced. Even in cats which by most authors are regarded as especially suitable for such research, only a catarrhal colitis at the most can be produced. In these animals no diphtheritic inflammation or ulcer formation can be produced whether the dysenteric excitant is introduced per os or per anum. The same is, however, observed in other infectious diseases, such as typhoid fever and cholera. The typhoid bacillus and cholera vibrio never produce the same lesions in animals as they call forth in men.

In 1896 Widal announced the so-called agglutination reaction produced by the serum of individuals sick with typhoid fever. This phenomenon I have employed in my researches respecting dysentery, upon the advice of Professor Kitasato. In 1897 I found a bacillus (B. dysenteriæ) in the stools and intestinal walls of dysenteric patients. This bacillus was present in all the cases of dysentery examined by me, but was never found in healthy individuals or those sick with other diseases. Furthermore it was plainly agglutinated by the serum of dysenteric patients and has since been accepted as the producer of dysentery. Flexner in 1900 found the same bacillus in dysenteric stools in Manila. Kruse, shortly thereafter, made a similar discovery in Germany. Subsequently (1901) Flexner isolated this microorganism from dysenteric stools in the United States. Deycke in 1901 in Constantinople obtained a bacillus from dysenteric stools whose morphology and cultural characteristics indentify it as B. dysenteriæ. Frosch, v. Drigalski, and Conradi during the epidemic of dysentery in Prussia, which was supposedly transmitted from China during the recent war, also isolated the same bacillus from dysenteric dejections. Very recently Foulerton has announced the isolation of the bacillus in eight cases of dysentery which originated among the English troops in South Africa and were transported to the vicinity of London. It is thus established that the B. dysenteriæ is the producer of the disease not only in Japan but also in America, Europe, and the Philippines.

Amœbic dysentery is observed principally in tropical countries as Egypt, Italy, Africa, Arabia, Southern China, Formosa (Japan), Philippines, etc. It is only occasionally found in the temperate zone as the United States, Prussia, etc. The researches of Flexner and Strong in Manila have materially increased our knowledge with respect to tropical dysentery. They have shown that in the tropics two types of dysentery are to be observed—the bacillary and the amœbic.

The first is produced by the B. dysenteriæ and usually runs an acute course. The second is chronic and shows the presence of no dysenteric bacilli, but the amœbæ are found in the dejections and in the submucous tissue of the dysenteric ulcers. Since, therefore, two forms of dysentery are to be observed in the tropics, it is evident that the so-called tropical dysentery has no place in the etiological classification of this disease. Strong divides the dysentery of the tropics into acute and amœbic types. Although the etiological foundation of the amœbæ is not as yet firmly established, at the present time it is best to divide dysentery into the two forms of bacillary and amœbic.

From the above résumé it is possible to form some opinion with respect to the geographical distribution of these types. The chief advances which are to be made in our knowledge of dysentery must come from the study of the disease in the tropics since there the two forms are in close proximity.

Bacillary dysentery is an infectious disease produced by the B. dysenteriæ. It asserts itself pathologically in the production of catarrhal and diphtheritic inflammation and the formation of necrotic ulcers in the intestine (usually the large intestine, but frequently also the small intestine). Clinically it is characterized by frequent slimy and bloody stools accompanied by tormina (colic) and tenesmus.

Bacillus Dysenteriæ.

Morphology.—Dysenteric bacilli are small plump rods with rounded ends very similar to colon bacilli. They are usually single, but occasionally occur in pairs. Their motility is less than that of the bacillus typhosus, so that they show only slight changes of position in the microscopical field. Their motion is thus apt to be confounded with molecular motion. There is no spore formation. Kruse regards the bacilli as non-motile. Flexner says that they are slightly motile but that this property is soon lost. As Flexner has pointed out, these differences of opinion with respect to the motility of the bacillus are probably due to the diverse conditions under which these microorganisms have been examined, such as the nutrient medium employed and the generation observed. The successful demonstration of flagella, however, absolutely proves that they are motile. On one occasion I have observed polar flagella in a stained preparation. Recently Vedder and Duval by the employment of Van Ermengen's method have demonstrated flagella in various cultures of this bacillus (Flexner's, Strong's, Kruse's, and my own). According to these authors the flagella are quite long (eight to ten times the length of the body of the bacillus), slightly spiral, and surround the entire body of the microorganism. The bacillus stains readily with the ordinary aniline dyes.

Gram's stain is not retained. They grow in the absence of oxygen but not so well as in its presence (facultative anaërobes). The optimum temperature is that of the incubator, nevertheless they grew tolerably well at the room temperature. Gelatin is not liquefied.

Cultural Characteristics. Gelatin Plates.—Deep colonies are round, pin-pointed, and possess sharp, well-defined borders. Under a low magnification they are of a brownish-yellow color with round or whetstone-like borders. Surface colonies are larger and show irregular

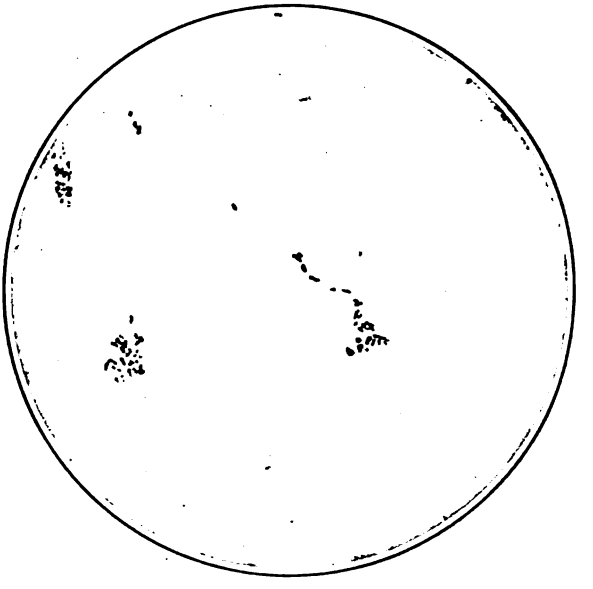


FIG. 43.—Bacillus Dysenteriæ.

edges. In plates of the ordinary ten-per-cent. gelatin they are often leaf-like in appearance. In fifteen to twenty per cent. gelatin, surface and deep colonies show practically an identical form.

Gelatin Stabs.—The development extends along the entire stab.

Agar Cultures.—Like the typhoid bacillus they show less growth than the colon bacillus. After twenty-four hours in the incubator they form small, thin colonies which are round and have a moist appearance when viewed obliquely. After several days they become thicker, of a grayish-white color, and show thread formation.

Agar Streaks.—They give an even development along the line of inoculation (typhoid bacilli give a broad growth below and a narrow growth above. This is never the case with dysenteric bacilli).

Glucose-agar.—A grayish-white growth along the entire line of inoculation. No gas formation.

Bouillon.—Even clouding with sedimentation. No pellicle and no indol production.

Glucose Bouillon.—No fermentation.

Peptone Solution.—No indol production.

Litmus Milk.—After one to three days in the incubator weak acid formation. After five to seven days alkaline reaction and a gradual increase in the brown color of the culture.

Potato.—The development is different according to the variety of potato used. At times no development can be seen by the naked eye. Often the growth is slight and of a brown or white color. If the potato is acid in reaction the growth is not perceptible. It is, however, apparent and brownish or white in color if the potato is cooked in a salt or soda solution and is hence alkaline or neutral in reaction. (The typhoid bacillus shows under the same conditions a similar growth.)

Involution Forms.—When B. dysenteriæ is cultivated upon agar which contains a large percentage of common salt, various involution forms are seen. Upon five per cent. NaCl agar such forms are especially prominent and appear as large irregularly shaped rods, often of spiral form, with bulbous ends. Their edges are irregular, and numerous prolongations of the body protoplasm are seen. They often are united in thread or chain-like formations. Shadow forms are frequently seen which contain numerous chromatic granules. The typhoid bacillus under identical conditions shows similar involution forms but they are less marked. Upon seven per cent. NaCl agar B. dysenteriæ continues to live but refuses to grow (also B. typhi) while B. coli grows fairly well and produces many branching involution forms not seen with B. dysenteriæ.

Resistance.—The B. dysenteriæ is killed by a 0.5-per-cent. carbolic-acid solution in six hours, by a one-per-cent. solution in thirty minutes, by a five-per-cent. carbolic acid or 1–200,000 bichloride solution instantly. In five-per-cent. alcohol it perishes in thirty minutes, in ten-per-cent. in five minutes. Exposed to direct sunlight it dies in thirty minutes. Drying in the air kills it after several days.

Animal Experimentation.—After the subcutaneous inoculation of small quantities of agar cultures *mice* die in some days greatly emaciated. Intraperitoneal inoculation of $\frac{1}{10}$ of a loop of a virulent fresh agar culture produces death in twenty-four hours. At autopsy there is found a scanty bloody exudate in the peritoneal cavity and a slimy mixture in the intestines. The liver and the spleen are usually normal.

Young guinea-pigs are killed in twenty-four hours by the intraperitoneal inoculation of $\frac{1}{3}$ of a loop of a highly virulent agar culture. (B. dysenteriæ very quickly loses its virulence.) At autopsy the

peritoneum is found markedly injected and in the peritoneal cavity there is an abundant bloody exudation. The contents of the intestine are slimy and bloody and microscopically there may be seen epithelium, vegetable cells, numerous red and white blood cells, and various bacteria. On the wall of the cæcum numerous hemorrhages are often present. If the animal is inoculated with a smaller quantity of culture, death is produced more slowly by marasmus.

Rabbits are very susceptible to B. dysenteriæ. The anatomical lesions accompanying an acute infection are similar to those found in guinea-pigs. As the result of chronic infection the animal dies of a high-grade marasmus.

Two cats (one 480 gm. and the other 700 gm.) were, as a preliminary, given one-half a drop of croton oil with the evening meal. On the following morning both animals passed fluid stools in which no dysenteric bacilli were found. An entire agar culture was then introduced into the stomach of the second animal by means of a catheter. While the first animal (the control) had entirely recovered from the diarrhœa, on the following day the second animal was still passing slimy gray stools. This diarrhœa lasted one week during which time the B. dysenteriæ was repeatedly isolated from the stools. The animal died in four weeks markedly emaciated. At autopsy the rectal mucous membrane was hyperæmic for a space of several centimetres. From the cæcum to the rectum the entire gut was filled with a slimy material containing many round, mucus-covered fæcal masses. The B. dysenteriæ was isolated in large numbers from the contents of the appendix and large intestine.

A dog of 1,750 gm. was taken from whose stools B. dysenteriæ could not be obtained, and an agar culture was introduced into its stomach. On the following morning the animal passed grayish-yellow fluid stools which contained many dysenteric bacilli. On the third day the dog refused food, had a yellowish, watery diarrhœa, and vomited frequently. On the fourth day the animal entirely refused food and had repeated attacks of vomiting. Death took place on the morning of the fifth day. At autopsy the upper part of the small intestine for a length of about 50 cm. was filled with slime. On the intestinal wall were several circumscribed hemorrhages of about 1 cm. in diameter. The mucous membrane of the large intestine was swollen and covered with slime. The rectum was relatively normal. The other organs showed no lesions. Dysenteric bacilli were numerous in the slimy contents of the small intestine. The blood and all the organs were sterile.

I have not been able in animal experimentation by the use of either dysenteric stools or pure cultures of the dysenteric bacillus to produce those lesions of the intestine which are commonly found in individ-

uals dead of dysentery. At the most in this manner can be produced only hyperæmia and hemorrhages in the intestinal mucous membrane of guinea-pigs, dogs, and cats.

Presence of B. Dysenteriæ in Dysenteric Patients.—In the latter half of the first week of the disease the B. dysenteriæ is present in almost pure culture in the fresh stools which consist exclusively of slime and blood from the intestinal lesions. In the beginning of the disease it is very difficult to obtain dysenteric bacilli from the fæces. This is, however, frequently successfully accomplished if at this period of the disease the stools are slimy. It is easily understood why dysenteric bacilli are found in the stools early in the disease while in typhoid fever the bacillus typhosus is first found in the fæces during the second and third clinical week, since the localization of the intestinal lesions in these diseases is different. In dysentery the higher the lesions are located (transverse and ascending colon, cæcum, and small intestine) the more difficult is the isolation of the specific bacillus from the fæces. The reverse also holds true. If the dejections become purulent the number of dysenteric bacilli markedly diminishes. In normal stools, yellowish or gray in color, they are entirely absent. In relapses they are frequently present in the fæces when they had previously disappeared. In such cases it is to be conceived that the development of the bacilli is favored by suitable conditions, and that under such they again vegetate. In short, the presence of dysenteric bacilli in the dejections corresponds to the morbid process and their number coincides with the stage of the disease.

In the intestinal mucous membrane dysenteric bacilli are very numerous or present in pure culture in fresh catarrhal or diphtheritic masses and in the deeper layers of the ulcerative lesions, while in the superficial layers of old lesions they are overgrown by colon bacilli and various other microorganisms. They are often found in the swollen mesenteric glands. On the other hand, I have never found them either microscopically or culturally in the liver or spleen. In five cases of parotitis which developed in the course of dysentery (generally from the third to the fifth week), I endeavored to isolate the dysenteric bacillus from the extirpated portions of the gland or from its secretion obtained by puncture, but the results were always negative. The urine, blood, and milk are always sterile. In considering the localization of the specific bacillus in dysentery it must be remembered that in this disease there are no enlarged spleen, no roseola, and no bone or bone-marrow inflammations.

The Relation of B. Dysenteriæ to the Blood of Dysenteric Patients.—That the blood of dysenteric patients during convalescence is able to agglutinate the B. dysenteriæ (so-called Widal reaction) I have proven by hundreds of observations. Some reactions are positive in 1 to 130

dilutions ($A_1 = 130$). Usually, however, the reaction is positive in 1 to 20 or 50 dilutions ($A_1 = 20$ to 50). Occasionally in mild dysentery the reaction is negative ($A_1 < 10$). It must be stated that in my agglutination tests I have always used the blood and never the serum since the former was the more convenient, being easily obtained from the lobe of the ear in a pipette, similar to that used in the enumeration of red blood cells, and immediately diluted 1 to 10. The agglutinating power of the blood is about one-half that of the serum. The agglutination tests conducted with the blood of persons sick with other diseases or healthy individuals were always negative, although such tests were tried (blood serum or blister exudate) in twelve healthy persons, sixteen cases of typhoid fever, three of intestinal catarrh, three of beriberi.

On the other hand, I have shown that the blood of a dysenteric patient gave a plain reaction eight months after recovery from the disease. Such an agglutination cannot, however, be employed for diagnostic purposes, since it is slight and in most cases negative.

According to Kruse the agglutination of B. dysenteriæ, as isolated by him, by dysenteric serum is more marked, being produced by 1 to 50 and in one case by a 1 to 1,000 dilution. Because of this difference in the agglutinating capability he regards his bacillus as different from mine. Unfortunately he has forgotten that the agglutinating capability of a bacillus varies according to its race and the media upon which it is grown (a fact already well established with respect to B. typhi). Furthermore, the agglutinating power of a serum varies with the character of the epidemic and perhaps also with the nationality of the patient. Especially must it be mentioned that the maximum limit of the agglutination varies according to the technique employed and the individual judgment of the observer. Vedder and Duval have said that there is no difference in the agglutination capabilities of various races of dysenteric bacilli (Flexner's, Kruse's, my own, etc.) when tested with an immune serum. I have shown that Flexner's and Kruse's bacilli were agglutinated by the serum of a dysenteric patient in Japan, and that therefore this test is sufficient to establish their identity with my own B. dysenteriæ.

Practical Application of the Agglutination Reaction to the Diagnosis and Prognosis of Dysentery.—The mere fact that at the first trial the blood of a dysenteric patient agglutinates B. dysenteriæ is not sufficient evidence that this microorganism is the cause of the disease since such an agglutination might be accidental. However, if such an agglutinating power of the serum increases in intensity with the duration of the disease, it is certain that this bacillus is the causative factor. The same has been especially emphasized by Förster with respect to the serum diagnosis of typhoid fever. He maintains that for a diag-

nosis of typhoid it must be shown that the agglutinating power of the serum is greater at the second than at the first examination. To this end I have undertaken agglutination tests in ten cases of dysentery at various periods during the disease and found that the agglutinating power of the serum is subjected to certain variations during the course of the disease and describes a characteristic curve. An example is here given:

Day of disease.	Agglutinating power of serum.	Clinical symptoms.
Sixteenth	$A_1 < 10$	First week—slimy stools, daily number twenty to thirty. Temp. 37°–37.5° C., tenesmus, pains in the left ileo-cæcal region.
Twentieth	$A_1 = 90$	Second week—slimy, bloody stools, daily number five to ten.
Twenty-fifth	$A_1 = 130$	Third week—yellow fluid stools, often bloody, daily number two to three.
Thirty-seventh	$A_1 = 100$	Fourth week—recovery.

In general, a positive agglutination reaction is first present in dysentery during the second or third week of the disease, during convalescence reaches its highest point, and then gradually subsides in intensity. Occasionally it first appears at the end of the sixth week. For these reasons the Widal reaction is of little value in the diagnosis of dysentery. In one case, which ran a chronic course and in which recovery took place during the sixth week, the agglutination reaction during the entire course was relatively weak. Three patients in whom the agglutination reaction increased in intensity only slightly from day to day died of marasmus. On the other hand, in three cases the agglutination reaction was negative until the beginning of the third week; toward the end of this week it increased rapidly in intensity and the patients rapidly recovered. In two mild cases the agglutination reaction was weak throughout the whole course of the disease. From these observations two prognostic facts may be deduced: (1) If the agglutination reaction quickly increases in intensity the prognosis is favorable. (2) The prognosis is unfavorable or doubtful (unless the disease is very chronic) if the intensity of the agglutination reaction does not increase, or if at all, but slightly.

Bacteriological Diagnosis of Dysentery.—The bacteriological diagnosis of dysentery is of only limited application because the isolation of the specific bacillus is very rarely successful in mild cases and during the first days of the disease. If, however, the localization of the process is in the lower portions of the large intestine the B. dysenteriæ is early present in the dejections, and is more easily isolated than the typhoid bacillus in typhoid fever. The dysenteric bacilli are especially numer-

ous in slimy dejections mixed with fresh blood. In the usual manner agar plates are made from such dejections. After twenty-four hours' incubation various colonies will have developed upon these plates. From such one selects those colonies which are the least developed and the most transparent and tests the microorganisms composing them as follows: (1) Agglutinating capability with immune serum. (2) Cultivation upon glucose-agar. (3) Cultivation in milk.

If the agglutination reaction is positive, no gas is produced, and milk is not coagulated, the microorganism is B. dysenteriæ. In dysenteric stools bacilli are frequently present which are agglutinated by both immune and normal serum, while the B. dysenteriæ shows the phenomenon only with immune serum and the serum of dysenteric patients. The former also produce gas and coagulate milk. Such microorganisms are also found in the fæces of those sick with other diarrhœas. The B. dysenteriæ is by cultural methods with difficulty to be differentiated from the bacillus typhosus. It may, however, be easily differentiated by its motility (the typhoid bacillus being very motile and the B. dysenteriæ only slightly so) and their specific agglutinating capabilities.

Proofs that B. Dysenteriæ is the Cause of Dysentery.—1. B. dysenteriæ is present in all cases of dysentery.

2. B. dysenteriæ is never present in other diseases or in healthy individuals.

3. The presence of B. dysenteriæ in the stools corresponds in degree with the intensity of the morbid process.

4. B. dysenteriæ is found abundantly or in pure culture in the deeper layers of the intestine, while in old ulcerative lesions or in the superficial layers of the intestine it is seldom found, being overgrown by B. coli.

5. The B. dysenteriæ or its toxins (filtrates of bouillon cultures) produce intestinal hemorrhages. In research animals (especially rabbits) subcutaneous hemorrhages and hemorrhages of the serous and mucous membranes are found similar in character to those observed in dysenteric patients and in the bodies of persons dead of this disease. I have observed a pregnant woman who developed dysentery and aborted at the seventh month. Extensive hemorrhages were present in the breast, intestines, and extremities.

6. B. dysenteriæ is agglutinated only by the blood of dysenteric patients; never by the blood of those sick with other diseases or of healthy individuals.

7. The agglutinating power of the blood of dysenteric patients varies with the course of the disease, and describes a characteristic curve which at the beginning quickly ascends, reaches its maximum as convalescence approaches, and then gradually descends.

8. Pfeiffer's reaction of B. dysenteriæ is, in dysenteric patients, especially marked during convalescence.

9. Immune serum is of prophylactic and therapeutic value in the treatment of dysentery.

10. The infection of men. An assistant of Flexner swallowed in the laboratory a bouillon çulture of the B. dysenteriæ, and after twenty-four hours experienced marked diarrhœa of a slimy and bloody character. Strong gave to a criminal under sentence of death, who was perfectly healthy and had never had dysentery, a small quantity of sodium bicarbonate and fifteen minutes later a bouillon culture of B. dysenteriæ in milk. Diarrhœa set in after twenty-four hours combined with moderate dysenteric symptoms and slimy and bloody stools. From the stools the B. dysenteriæ was isolated. Two cases of infection also occurred among workers in Kruse's laboratory.

Epidemics of Dysentery in Japan.

The commencement of epidemics of dysentery in Japan is shrouded in mystery. The scientific name "Sekiri" signifies "red diarrhœa" and was transported from China. The popular name is "Akahara." It is widely diffused and well known to old persons. A species of herb known as "Gennoshoko" (Germanium nepalens) is far famed as a popular remedy; even peasants and mountaineers are aware of its value and its method of use. Its chief constituent is tannic acid. From these facts we may conclude that the commencement of the epidemics of dysentery in Japan dates back many hundreds of years.

The most recent large epidemic of dysentery, which in Japan annually for twenty years has claimed many thousands of victims, began in the southwest province (Kiushiu). It spread eastward and northward until at present the entire country is suffering from the pestilence. There is no province in which the disease is not present, for in all the provinces one meets annually a greater or smaller number of cases of this disease. The centre of the epidemic, however, has moved gradually from south to north and has during the last few years reached the northeast provinces (Niigata, Nagano, Fukushima, Iwate, and Aomori-Ken).

Many think that the dysenteric producer has entirely vanished from those regions which were once infested with the disease. I do not believe that such is the case. The epidemic does not recur in the following year because the susceptible individuals are greatly decreased in number or have entirely vanished. The specific microorganisms can during the winter exist outside of the human body, and again multiply in the healthy body. They must surely be the cause of the epidemic the following year. We meet often during the winter patients who

suffer from mild diarrhœa of a moderate slimy character. Probably they suffer from mild dysentery, and, unfortunately, if neglected, often unconsciously disseminate the microorganisms for the next epidemic.

The official statistics regarding the mortality and morbidity of the disease in the entire kingdom of Japan since 1878 are as follows:

Year.	Number of cases.	Number of deaths.	Percentage of deaths.	Year.	Number of cases.	Number of deaths.	Percentage of deaths.
1878.....	1,098	181	16.5	1890.....	42,633	8,706	20.4
1879.....	8,169	1,477	18.8	1891.....	46,358	11,208	24.2
1880.....	5,047	1,305	25.8	1892.....	70,824	16,844	23.7
1881.....	7,001	1,837	26.2	1893.....	167,305	41,282	24.7
1882.....	4,330	1,313	30.2	1894.....	155,124	38,089	24.5
1883.....	21,173	5,066	23.9	1895..... ...	52,711	12,959	24.5
1884.....	22,524	5,989	26.6	1896.....	85,876	22,356	26.0
1885.....	47,183	10,627	22.5	1897..... ...	91,077	23,189	25.4
1886.....	24,326	6,839	28.1	1898.....	90,976	22,392	24.6
1887.....	16,149	4,287	26.4	1899.....	108,713	23,763	23.8
1888.....	26,815	6,576	24.6	1900.....	46,236	10,265	22.1
1889.....	23,878	5,960	26.8				

The epidemics generally begin in Japan in June and during August, September, and October reach the maximum; they then quite rapidly subside. During the winter the disease does not entirely disappear and cases are occasionally seen.

Year 1899.	Number of cases.	Number of deaths.	Percentage of deaths.	Year 1899.	Number of cases.	Number of deaths.	Percentage of deaths.
January.....	150	50	33.3	July.....	19,113	3,168	16.5
February	100	58	58.0	August.....	27,575	6,039	22.0
March.....	103	20	19.4	September..	30,210	6,739	22.3
April.....	147	29	19.7	October	21,733	4,951	22.8
May	870	115	13.2	November ..	3,877	1,549	42.8
June	4,089	568	13.8	December ..	746	469	63.0

As these tables show the mortality in the beginning of the epidemic (May, June, and July) is low, and during the winter considerably higher. It is of course to be understood that the cold climate during November and December exerts an unfavorable influence upon the severe and chronic cases. It must also be observed that the morbidity of the disease during the interval (January, February, March, and April) is not accurately appreciated, so that the mortality at this time may be considerably higher than it appears to be.

Dysentery often recurs two or more times in the same individual. The immunity conferred by the disease is therefore insignificant, and usually entirely vanishes after one year. A fairly permanent immunity is conferred by typhoid infection, so that one rarely observes the

disease twice in the same individual. It is to be conceived that in dysentery a *locus minoris resistentiæ* is left in the intestine, which probably favors the subsequent infection. According to Ogata the cases of secondary infection in the epidemic of 1900 in Fukuoka-Ken were as follows:

Among 25,279 cases: Second attack in 700 (2.7 per cent.); third attack in 81 (0.32 per cent.).

According to the official statistics in Yamaguchi-Ken they were as follows:

Among 1,118 cases: Second attack in 29 (2.5 per cent.); third attack in 3 (0.3 per cent.).

Very few cases of dysentery recur the following year. In the epidemic of 1899 in Kanagawa-Ken, among 2,800 cases I observed only one such instance. In a small city (Nobechi) in Aomori-Ken, of 9,000 inhabitants an extensive epidemic of dysentery occurred in two succeeding years; over 400 cases in 1900 and over 200 in 1901. Among the latter there were only three who had suffered from the disease in 1900.

Pathological Anatomy.

The infection with dysentery takes place by the mouth. The dysenteric bacilli remain in the folds of the intestine (usually the large intestine) and multiply under favorable circumstances, among which may be mentioned constipation and intestinal disturbances. The mucous membrane reacts by inflammation, which may be catarrhal, hemorrhagic, or diphtheritic, according to the stage and grade of the process. The croupous-diphtheritic infiltrated mucous membrane becomes necrotic and thus ulcers are produced. This process rapidly extends and soon the entire contiguous mucous membrane is covered with ulcers. The intestinal wall becomes thickened on account of the marked infiltration. The small intestine is also sometimes involved and shows lesions similar to those of the large intestine. I have observed a case in which the small intestine was involved for a space of nearly 1 mm. above the ileo-cæcal valve and entirely ulcerous and diphtheritic; the wall of the colon was thickened. The peritoneum is also inflamed and adhesions are frequently present. Ecchymoses are present in the serous membranes in severe cases. Constipation favors infection and the multiplication of the dysenteric bacilli. For this reason the first lesions of the intestine are usually produced in the sigmoid flexure, rectum, flexura lienalis and hepatica, valvula Bauhini, and cæcum. If the lesions of the small intestine or cæcum are suitably localized the corresponding mesenteric glands will become swollen and secondarily infected as in typhoid fever. The spleen is never involved. The dysenteric bacillus does not probably enter the

general circulation. That such is the case is apparent from the fact that dysentery is never complicated by roseola, pneumonia, osteomyelitis, or periostitis. Parotitis is occasionally seen as a complication, but its connection with B. dysenteriæ is not clear, inasmuch as it may result from a secondary infection by other organisms present in the mouth. The latter is most probably the case.

The histological changes of the intestine predominate in the membrana mucosa, the submucosa, and the muscularis. The mucous membrane shows a coagulation necrosis with a fibrinous exudate and polymorphous cells. The submucosa is usually very much thickened. In certain places of the submucosa, especially in the deeper layers, there is a marked cell infiltration. The blood-vessels and capillaries are dilated and filled with blood cells. In various places hemorrhages of various degrees of intensity are present. The muscularis does not usually show much change, but occasionally infiltration and hemorrhages are present.

Numerous bacteria are found in the inflamed mucous membrane. These are especially numerous in the necrotic membrane. They are usually bacilli, but cocci are also found. In the deeper layers the bacilli are found in small numbers, but in the glands, between the gland cells and in the glandular stroma, they are numerous. Cocci are never found in these locations. In the submucosa and often in the muscularis the cell infiltration is accompanied by the presence of numerous bacilli. The bacilli seen in the deeper layers of the intestinal wall cannot be differentiated morphologically as the B. dysenteriæ; but transplantations from these regions show the presence of that organism in pure culture.

General Symptomatology.

The incubation of dysentery is generally three to eight days. In a case reported by Lemoine, in which infection took place by the rectum from the use of a chamber containing dysenteric stools, the incubation was twenty-four hours. The experimentally infected cases which were observed by Flexner and Strong in the laboratory showed an incubation of twenty-four to forty-eight hours.

Dysentery begins with diarrhœa and colic. At the onset the dejections are of the ordinary diarrhœal character, and contain only small quantities of slime. Abdominal pains and tenesmus soon develop. As a rule, on the second day the stools become slimy and bloody in character, and very soon pure slime and blood only are passed. They then possess a characteristic appearance. Usually the daily number of stools is from twenty to sixty, but quite frequently it is over one hundred. Tenesmus is very continuous, and so intense that the anus

and the rectum frequently become prolapsed and fæcal incontinence supervenes. The infiltrated intestine can be plainly felt through the abdominal wall, and such a procedure causes the patient great pain. The body temperature ascends generally to between 38° and 39° C.; not infrequently it exceeds 40° C. The urine is decreased in amount. The appetite vanishes. Generally in the second or third week the symptoms gradually improve. The stools become purulent or fæcal, and in severe cases they become gangrenous or putrid in character. This, as a rule, precedes a fatal termination.

The general symptoms of dysentery are due to the absorption of products which result from the solution of the bacilli themselves within the tissues and not to toxins excreted by the organisms. In mild cases fever and general indisposition are absent, but they are never failing symptoms in cases of medium severity. That the general symptoms are not so prominent as in typhoid fever is to be ascribed to the localization of the lesions. If lesions are present in the upper portion of the large intestine or in the small intestine, various intoxication symptoms are present, such as fever, headache, general malaise, muscular pains, epigastric oppression, sleeplessness, numbness, stupor, delirium, etc. If such symptoms are present it is customary to speak of typhoid dysentery. The rapid emaciation observed is not to be exclusively ascribed to the diarrhœa and inanition, but is partly due to intoxication. The inoculation of animals (especially rabbits and guinea-pigs) with toxins of the B. dysenteriæ (cultures sterilized by heat or filtered through a Chamberland filter) regularly produces marked emaciation. Ecchymoses are frequently present upon the epigastrium, chest, or inner surfaces of the upper and lower extremities, in the later and severe stages of the disease.

As has already been said, the intestinal lesions are principally located in the flexures. This is without doubt due to the fact that the mucous membrane in such locations is extremely susceptible to mechanical irritation and hence is especially suitable for the development of dysenteric bacilli. The involvement of the lower portion of the small intestine is usually secondary, but it is very probable that there do occur primary lesions in this location. As in typhoid fever, the usual seat in dysentery of the lesions in the small intestine is the lower portion of the same. The valvula Bauhini is frequently affected, being ulcerated and often entirely destroyed. As a rule, the cæcum and valvula Bauhini are extensively diseased, the intestine above being progressively less and less involved. The anatomico-histological changes in the small intestine are entirely similar to those above described for the large intestine. Many mesenteric glands are enlarged and merely hyperæmic as in typhoid. Following the healing of the ulcers the lumen of the intestine is narrowed by cicatrization. This

is "entero-dysentery," which I have thus named in order to separate it from "colo-dysentery," in which the lesions are localized in the large intestine and rectum.

The symptoms of entero-dysentery are somewhat different from those of colo-dysentery. In the former tenesmus is absent and the stools are not so frequent, but very voluminous. No incontinence of fæces is present. Tenesmus is always a sign that the rectum is involved. Very prominent are the toxic symptoms which have been described above in connection with the so-called typhoid dysentery. The prognosis of entero-dysentery is always serious. Its treatment requires great care. It is apparent that the differentiation between entero- and colo-dysentery is very important from pathological, clinical, therapeutic, and prognostic grounds.

In most instances the disease begins in the lower portion of the large intestine (sigmoid flexure and rectum) and gradually extends upward. There is, however, no doubt but that the lesions can primarily arise in various portions of the small and large intestine when suitable conditions are present for the multiplication of the bacilli and the inoculation of the intestinal wall. When the primary lesion is situated in the ileum or upper portion of the large intestine and the process advances downward, I speak of "descending dysentery" in contradistinction to "ascending dysentery," in which the reverse is the case and the primary lesion is situated in the lower portion of the large intestine, the process extending upward. The latter form is usually met with. It is easy to understand that the prognosis is worse in ascending dysentery than in descending.

Complication and Sequelæ.

Parotitis is often present in severe cases and in moderate cases which run a chronic course. It is usually bilateral and appears during the third and fifth weeks of the disease. Unilateral parotitis is seldom seen.

Ascites is often seen in debilitated patients or during convalescence, and is frequently combined with general dropsy.

Beriberi is often observed as a complication in Japan.

I have seen *abscesses* in two cases. In the first in the upper portion of the rectus abdominalis muscle, and in the second in the gluteal region. In both cases the lesion appeared during convalescence.

Abscess of the liver never occurs in bacillary dysentery.

Arthritis I have never observed.

Differential Diagnosis of Amœbic and Bacillary Dysentery.

Amœbic and bacillary dysentery must be differentiated etiologically, clinically, and anatomically. The following are the most important points in such a differentiation:

1. Amœbic dysentery usually runs a chronic course.

2. In amœbic dysentery no dysenteric bacilli can be found. Since in certain countries, as the Philippines, amœbic and bacillary dysentery both occur, it is possible that mixed infections of the two forms may take place.

3. In amœbic dysentery toxic symptoms are not observed, such as fever (expect when liver abscess or pyæmia is present), general malaise, headache, anorexia, rapid emaciation, hemorrhages, or various nervous symptoms.

4. In bacillary dysentery liver abscess is never present, but it is a very frequent complication of amœbic dysentery.

5. The small intestine is frequently affected in bacillary dysentery (entero-dysentery), while in amœbic dysentery the small intestine is never involved.

6. The anatomical processes are different. According to Kartulis and Kruse the edges of the ulcer are peculiarly undermined in amœbic dysentery, while in bacillary dysentery this is never the case and the ulcers are situated on the surface of the folds of mucous membrane.

Prognosis.

In considering the prognosis of dysentery the localization of the lesions in the intestines should be first considered:

Localization of lesions.	Symptomatic Treatment.			Serum Treatment.		
	Number of cases.	Number of deaths.	Percentage of deaths.	Number of cases.	Number of deaths.	Percentage of deaths.
Sigmoid flexure and rectum.....	62	6	9.7	80	2	2.5
Descending colon.....	94	49	52.1	90	8	8.8
Ascending and transverse colon...	4	4	100.0	5	0	
Entire colon.....	17	15	88.2	8	6	75.0
Entire large and small intestine...	1	1	100.0	10	4	40.0

This table shows that the prognosis is dependent upon the localization of the lesions. If these are limited to the sigmoid flexure or rectum the prognosis is favorable. If, however, the transverse and ascending colon or the small intestine become involved, the prognosis is very unfavorable. The higher the lesions are situated in the intestine the more unfavorable is the prognosis. For this reason the first

principles of treatment in dysentery comprise endeavors to limit the upward extension of the process and purgatives and enemata should be immediately ordered.

Nervous symptoms and other toxic appearances set in when the upper portion of the large intestine or the small intestine becomes involved. They constitute a very unfavorable sign, and such cases usually end fatally. Serum treatment in such cases is not entirely without avail. Symptomatic treatment gives much inferior results, as the following table shows:

Symptoms.	Symptomatic Treatment.		Serum Treatment.	
	Number of cases.	Number of deaths.	Number of cases.	Number of deaths.
Nervous symptoms	30	25	22	11
Vomiting	24	20	16	9
Singultus	13	11	9	8
Epigastric oppression	12	11	15	7
Ecchymoses	8	7	1	1

Treatment.

Serumtherapy of Dysentery.—*Immunization of Horses against Dysentery.*—An agar culture of the B. dysenteriæ which has been maintained at the incubator temperature for twenty-four hours is emulsified in normal saline solution and heated at 60° C. for one-half an hour. This mixture is then inoculated subcutaneously into horses in the usual manner, beginning with small doses, which are gradually increased in amount. The immunization can be more easily produced if immune serum is added to the emulsion of the dysenteric bacilli, because abscesses which reduce the vitality of the animal are often produced at the site of inoculation when bacilli alone are employed.

Animal Experimentation.—Into research animals, which have been inoculated twenty-four hours previously with a small quantity of immune serum, five times the minimum fatal dose of the culture is injected. The minimum fatal dose for guinea-pigs is one-third of a loop, for mice one-thirtieth of a loop (a loop = 1.2 mgm.). By intraperitoneal inoculations of these doses the animals (guinea-pigs of 250–300 gm., mice of 10–15 gm. body weight) die in twenty-four hours. Such experiments are the following:

Mice (weight).	Amount of immune serum.	Quantity of culture inoculated.	Death.
9 gm.	0.001 c.c	Five times minimum dose	Inside of twenty hours.
8 gm.	.002 c.c	Five times minimum dose	Sickened and recovered.
10 gm.	.003 c.c	Five times minimum dose	Remained alive.
8 gm.	.004 c.c	Five times minimum dose	Remained alive.
9 gm.	Normal serum .005 c.c.	Minimum dose	Inside of twenty hours.
10 gm.		Minimum dose	Inside of twenty hours.

The therapeutic animal experiments were carried out as follows: The guinea-pigs were inoculated subcutaneously with the cultures in the abdominal wall, and after various periods of time the serum was injected. The results obtained can be seen in the following tables:

Number.	Weight of guinea-pig.	Amount of culture (subcutaneous).	Serum.	Time from infection to serum inoculation.
1.....	300 gm.	Two loops.	Normal serum, 1 c.c.	Immediately.
2.....	290 gm.	Two loops.	Immune serum, 1 c.c.	Five hours.
3.....	285 gm.	Two loops.	Immune serum, 1 c.c.	Ten hours.
4.....	280 gm.	Two loops.	Immune serum, 1 c.c.	Fifteen hours.
5.....	250 gm.	Two loops.	Immune serum, 1 c.c.	Twenty hours.

The observations during the course of the experiments were as follows:

Day of sickness.	No. 1.	No. 2.	No. 3.	No. 4.	No. 5.
1	Weight, 300 gm....	Weight 290 gm	Weight 250 gm ..	Weight 280 gm ..	Weight 250 gm.
2	Weight 256 gm.; site of inoculation markedly infiltrated.	Weight 285 gm.; local infiltration; animal lazy.	Weight 245 gm.; slight infiltration; animal lazy.	Weight 250 gm.; extensive infiltration.	Weight 205 gm.; extensive infiltration; animal lazy.
3	Weight 230 gm.; animal lazy.	Weight 230 gm.; extensive infiltration.	Weight 220 gm.; extensive infiltration.	Weight 225 gm.; animal lazy.	Weight 180 gm.; animal emaciated.
4	Weight 220 gm.; marked emaciation.	Weight 212 gm.; as yesterday.	Weight 216 gm.; animal lazy.	Weight 218 gm.; as yesterday.	Weight 175 gm.; animal comatose.
6	Weight 196 gm., marked emaciation.	Weight 220 gm.; infiltrated place ulcerated.	Weight 224 gm ..	Weight 236 gm ..	Weight 162 gm.
7	Weight 170 gm.; death.	Weight 226 gm.; ulcerated surface dried; healed.	Weight 230 gm...	Weight 248 gm.; infiltrated place ulcerated.	Weight 150 gm.; marked emaciation; death.
8	.....	Weight 230 gm.....	Weight 224 gm ..	Weight 236 gm.; healed.	
12	.....	Weight 250 gm.; well.	Weight 236 gm.; well.	Weight 250 gm.; well.	

The control animals which received the cultures and normal serum died on the seventh day, while other animals which received 1 c.c. of immune serum from five to fifteen hours after infection became sick, but after one week had entirely recovered. The animal which was inoculated with the immune serum twenty hours after infection was not saved, and died like the control animal on the seventh day.

Practical Serum Treatment.—Dysenteric serum like typhoid serum is bactericidal, but in practice the former gives much better results than the latter. According to my opinion this is due to the localization of the lesions and the toxic symptoms. In dysentery the lesions are usually localized in the rectum and lower portion of the large intestine, whose physiological function is principally mechanical, and where absorption of the food does not take place as in the small intestine. The toxic symptoms are intimately connected with this locali-

zation, against which bactericidal serum is valueless. Such symptoms in dysentery are happily less prominent than in typhoid fever. This is the chief reason for the favorable influence of dysenteric serum. This conception also accounts for the very unfavorable prognosis in enterodysentery.

In accordance with my researches I have formulated the following rules for the administration of dysenteric serum for use in the Institute for Infectious Diseases in Tokyo:

1. In mild cases the serum is inoculated once in a dose of 6 to 10 c.c.

2. In cases of medium severity the serum is twice inoculated in doses of 10 c.c. The interval is from six to ten hours.

3. In severe cases the greatest quantities of serum are inoculated (about 60 c.c.). The daily dose does not, however, exceed 20 c.c.

By serum treatment the disease in its first stages is quickly cured or markedly ameliorated. In advanced or inflammatory stages the effects produced are about as follows: The number of stools is markedly diminished (generally reduced by halves for three successive days followed by rapid recovery), the tormina and tenesmus decrease, the blood in the stools diminishes or entirely vanishes, the abdominal pains lessen, the fever vanishes, the appetite increases, and the general condition is much improved. In the ulcerative stage the action of the serum is not so pronounced as in the earlier stages, nevertheless healing of the ulcers with cicatrization often takes place. In such cases the fever is reduced, the number of stools is markedly diminished, the general condition is improved, and the appetite increases. In this stage even the results obtained are far better than those given by any other method of treatment.

By the serum treatment the course of the disease is shortened in those who recover and lengthened in those who die. Of the 510 cases which I have treated (298 with serum and 212 with drugs) the entire course (counting from the beginning of the sickness to the discharge from the hospital) was on the average as follows:

	Recovered.	Died.
Serum treatment	25 days.	16 days.
Symptomatic treatment	40 days.	11 days.

The mortality of dysentery varies according to the climate, the epidemic, etc. In order to estimate properly the value of the serum treatment I will here record the mortality in hospital treatment.

The mortality by the use of the serum treatment was reduced one-third below that given by symptomatic treatment, and was less than one-half the minimum obtained by such treatment.

MORTALITY IN HOSPITAL TREATMENT.

Year.	Hospital.	Treatment.	Number of cases.	Deaths.	Per-centage of deaths.
1895	City Hospital.....	Symptomatic..	88	22	55.0
1896	City Hospital I.....	Symptomatic..	221	86	39.0
1896	City Hospital II.....	Symptomatic..	6	2	33.3
1897	City Hospital I.....	Symptomatic..	336	143	42.4
1897	City Hospital II.....	Symptomatic..	4	1	25.0
1897	City Hospital III.....	Symptomatic..	767	304	39.6
1897	Institute for Infectious Diseases.	Symptomatic..	34	8	23.5
1898	City Hospital I.....	Symptomatic..	178	78	42.0
1898	City Hospital II.....	Symptomatic..	51	20	37.7
1898	City Hospital III.....	Symptomatic..	385	141	36.6
1898	Institute for Infectious Diseases.	Serum.....	65	6	9.2
1899	City Hospital I.....	Symptomatic..	98	32	32.6
1899	City Hospital II.....	Serum.....	88	119	12.5
1899	City Hospital III.....	Symptomatic..	481	105	22.0
1899	Institute for Infectious Diseases.	Serum.....	105	5	8.5
1900	Institute for Infectious Diseases.	Serum.....	40		12.5

Non-Specific Treatment.—In the treatment of dysentery, independent of whether or not serumtherapy is employed, suitable cathartics and enemata should always be administered, since these tend to limit the upward extension of the disease. For this purpose I generally order 0.5 gm. of calomel, to be given twice, or 10 to 15 c.c. of castor oil, which is to be given but once. Thereafter enemata of one-per-cent. saline or soda solution should be given once or twice daily. Combined with the serum treatment I generally order alkaline or acid drinks and red wine. On the other hand, I have frequently used the various drugs which are recommended, such as ipecacuanha, tannin, bismuth subnitrate, dermatol, naphthol, antidysenteric pills, salol, etc.; also as enemata solutions of tannin, acetic acid, salicylic acid, quinine, thymol, creolin, naphthalin, etc. According to my experience dysenteric patients, like typhoid patients, are frequently injured by excessive medication, and many drugs which have been more or less strongly recommended are valueless and frequently detrimental.

Illustrative Cases.

CASE I.—Kimura, aged 26 years. Present sickness began on September 30th, 1898. Admitted into hospital October 1st. Duration of disease fifteen days. Recovery.

History.—At midday on September 30th the patient was seized with abdominal pains, and toward evening with a diarrhœal passage and tenesmus. The stools were slimy. The appetite was poor.

Present Condition.—October 1st.—The patient is fairly well nourished and of medium size. Tongue coated. Anorexia. Temperature, 37.9° C. (100.2° F.). Complains of abdominal pains upon pressure. Tenesmus. Slimy, bloody stools. Number of stools about three per

hour (about fifty in twenty-four hours). At 9:30 P.M. 20 c.c. of dysenteric serum was inoculated.

October 2d.—Last night the sleep was greatly disturbed. Tongue more coated. Appetite somewhat better than yesterday. Temperature, 38.6° C. (101.5° F.). The colic is considerably reduced. No tenesmus. The sigmoid flexure is swollen and can be plainly felt. Abdominal pains are still produced by pressure. Stools reduced to twenty in the last twenty-four hours. The stools consist of slime, blood, and a small quantity of pus.

October 3d.—Temperature normal. Tongue less coated. Appetite good. The sigmoid flexure is not painful upon pressure but is still swollen. The stools are slimy and of a grayish purulent appearance. They contain no blood. Number of stools in twenty-four hours, nine.

October 4th.—Appetite very good. The sigmoid flexure is apparently normal upon palpation. Number of stools in twenty-four hours

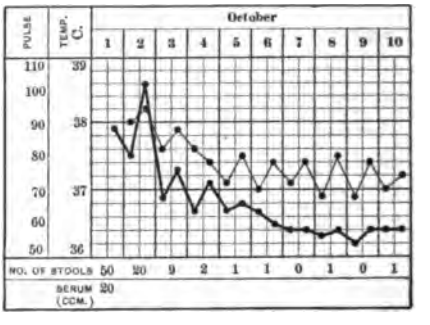


CHART 1.—Case I., Kimura.

two. They are yellowish, soft, and contain a very small quantity of blood and slime.

October 5th.—The stools are yellowish, soft, and contain a very little slime. Number in twenty-four hours, one.

October 6th.—All symptoms have disappeared.

October 13th.—Discharged cured.

CASE II.—Saito, aged 43 years. Present sickness began on August 19th, 1898. Admitted to hospital August 20th. Duration of disease, eighteen days. Recovery.

History.—On the 18th of August the patient was seized with headache without any apparent cause. On the evening of the 19th a violent diarrhœa set in. The stools were passed hourly for about twenty times and were accompanied by colic. On August 20th the number of stools was increased to about three per hour and were colored with blood.

Present Condition.—August 20th.—The patient is well nourished and of a powerful build. Complains of headache and intense thirst. Temperature, 39.4° C. (102.9° F.). Tongue coated with a thick white layer. Conjunctivæ slightly injected. Appetite poor. Spleen slightly enlarged (three years previously the patient has suffered from diarrhœa and since that time has had repeated attacks). Ileo-cæcal re-

gion normal. The sigmoid flexure is swollen and can be plainly felt. Pressure upon it elicits marked pain. Tenesmus fairly well marked. The stools are slimy and bloody. Number of stools, about eighty per day. At midday 10 c.c. of dysenteric serum was inoculated subcutaneously. The same was repeated at 3 P.M.

August 21st.—The temperature is reduced to 37.5° C. (99.5° F.). The patient feels considerably better. Appetite improved. The character of the stools is the same as yesterday, but the number is reduced to fifty-four.

August 22d.—Temperature normal. Appetite very good. Colic much reduced. The stools are slimy and mixed with a very small quantity of blood. Number of stools in twenty-four hours, thirty-five. Amount of urine considerably increased.

August 23d.—Tongue normal in appearance. Number of stools in twenty-four hours, twenty-three; they contain no blood.

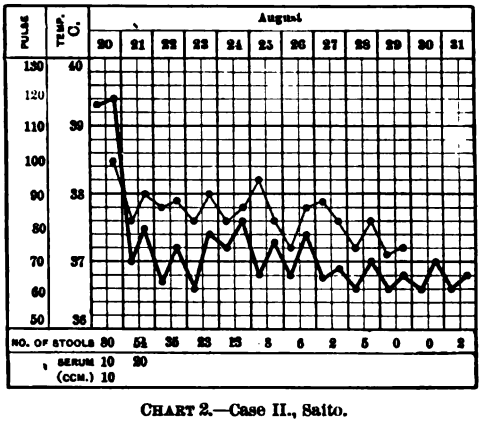


CHART 2.—Case II., Saito.

August 24th.—General condition very good. The sigmoid flexure is not tender upon pressure. No tenesmus. The stools are slimy. Number in twenty-four hours, thirteen.

August 25th.—Appetite very good. Tongue normal. The stools are somewhat purulent. Number in twenty-four hours, eight.

August 27th.—Urticaria has developed at the site of the inoculation. Spleen is normal in size. The stools contain neither blood nor pus. Number in twenty-four hours, two.

August 28th.—The urticaria has disappeared. After an enema a yellowish soft stool was passed.

September 5th.—Discharged cured.

CASE III.—Miki, 13 years old. The attack began on September 4th, 1898, and the case came under treatment two days later. Duration of the disease, twenty-three days. Recovery.

History.—The first symptoms were colic and malaise. As the boy had been constipated he was given a laxative which was followed by one stool. On the following day (September 3d) he had diarrhœa (about twenty stools) accompanied with tenesmus, and the day after that the discharges became bloody.

Present Condition.—The patient is fairly well nourished. Temperature 37.8° C. (100° F.), pulse 128, small, and of low tension. The tongue is covered with a thick white fur, there is anorexia, and the child complains of nausea. The sigmoid flexure feels thickened and is quite tender on pressure. Borborygmi are present. The stools contain mucus, pus, and considerable blood. Number of stools about sixty on the day of admission. At two o'clock in the afternoon an injection of 20 c.c. of dysenteric serum was administered.

September 5th.—The patient complains of severe pain in the umbilical region. The stools contain mucus, pus, and blood; number in the day, fifty-three.

September 6th.—Number of stools, thirty-seven. An injection of 20 c.c. of serum was given.

September 7th.—Temperature, 39° C. (102° F.). Less abdominal pain. The number of stools was forty-one; they contained but little blood. Another injection of 10 c.c. of serum was given.

September 18th.—One normal stool was passed.

September 21st.—The patient had an eruption of urticaria covering the entire body, and the temperature rose to 38° C. (100.4° F.).

September 23d.—The urticaria has disappeared.

September 24th.—The patient was discharged cured.

CEREBROSPINAL MENINGITIS.

BY

A. NETTER,

PARIS.

History and Geographical Distribution.—The epidemic of meningitis to which we called attention in 1898 has since increased very markedly all over the world. In France, it appeared first in Paris, Lille, and Bayonne, then in Arras, Avignon, Marseilles, Riom, Rennes, and crossed the Mediterranean to exhibit itself in Constantine and Algiers. In Germany, in Austria, and in Holland cases were fairly numerous. England, and more especially Ireland, were reached in 1900 and 1901. The Scandinavian countries, Italy, Greece, and Roumania also had some cases. India, South Africa, and even Australia were not exempt from the scourge. The various States of the American republic have paid their tribute to the epidemic from the Atlantic to the Pacific oceans, and from their northern boundaries to the shores of the Gulf of Mexico.

Bacteriology.

Numerous experiences have established the fact of the influence of the microbes which were mentioned in the previous article—the pneumococcus, the encapsulated streptococcus of Bonôme, and the intracellular diplococcus. Organisms which appear to be identical with Bonôme's organism, a variety of pneumococcus, have been isolated in Paris by Besançon and Griffin, Chantemesse and Millet, Thiercelin and Rosenthal. These writers all agree in recognizing the analogy between the cultures of their microbe on gelose, and those of the pneumococcus, pointing out the arrangement in more or less elongated chains, the possibility of developing the cultures on gelatin, the intermediate position between the pneumococcus and the streptococcus (enterococcus of Thiercelin), and the lessened pathogenic action in mice. All these properties are those which, following Bonôme, we have attributed to the microbe isolated by us at the beginning of the Paris epidemic in 1898, and which by a series of inoculations and cultures we have been able to transform into a pure pneumococcus. In

many cases we have had occasion to isolate the diplococcus intracellularis of Weichselbaum, which since the publication of our article has been studied by a number of authors, more especially by Osler, Albrecht and Ghon, Jündell, and others.

The micrococcus of Weichselbaum possesses certain rather special characteristics, which do not consist alone in the occurrence of diplococcus forms, viewed in plane surface (coffee grains), and their frequent presence in the bodies of the cells. They consist in the first place in the decoloration which is constant by Gram's method, the difficulty experienced in obtaining cultures, unless, as in the case of the gonococcus, we add serum to the culture medium, and the impossibility of developing them at a temperature below 24°. On agar the colonies appear at first merely as a fine transparent mist recalling the cultures of pneumococcus. These colonies spread and thicken, taking on a brilliant grayish-white tint. With age they become brownish. Development is more rapid on Loeffler's serum, which is the best culture medium for them. Upon one point only we must complete or correct the first description given by Weichselbaum—the micrococcus can be developed on bouillon. If the culture is not disturbed a mist appears on the surface of the fluid at the end of a few days.

Although at the ordinary temperature cultures quickly lose their property of enduring transplantation, those kept in the oven can be successfully sown even after the lapse of a long time, so that the same microbe has been known to be cultivated for more than four years. In old, and even in recent cultures, certain microbes acquire proportions so abnormal as to make them look like yeast. Inequality is rather a characteristic of this species.

These are the chief properties of the Weichselbaum microbe, which correspond absolutely to those given by a number of writers, especially Councilman, Mallory, and Wright (Boston), Albrecht and Ghon (Vienna and Trifail), Faber (Copenhagen), Looft and Lie (Bergen), Jündell (Stockholm), Netter, Griffon (Paris), Engelhardt and d'Astros (Marseilles), Billet (Constantine), Concetti (Rome), etc. On the other hand, it is not possible at once to accept the descriptions given by Jaeger, Heubner, Pfaundler, and Hunter and Nuthall, as relating to this same microbe. The ones they describe are like the first in the coffee-grain appearance, but in the cultures they are apt to dispose themselves in clusters and chains, and the stain persists by the Gram method. They produce rapid and abundant cultures, and can sometimes be developed on gelatin. Pfaundler, who was the first to call attention to the difference between these two types of microbe after the observation of cases similar to those described by Weichselbaum, and others recalling those of Jaeger and of Heubner, holds that they are merely varieties of the same microbe. Albrecht and Ghon, who

had the opportunity of comparing Weichselbaum's microbe with the cultures of Heubner, of Jaeger, and of Pfaundler, do not admit this relationship, and believe that the microbes are of different species. It would almost seem that they are not far from admitting that, as Hünermann stated, the Jaeger microbe is a variety of staphylococcus, that there might even have been accidental contamination of the cultures, and that the Heubner and Jaeger microbes really play no part at all in cerebrospinal meningitis; in fine, that the investigators saw the true microbe, but cultivated merely an accidental saprophyte. This is the observation made by Jaeger to Hünermann. It is perhaps permissible to wonder whether the different properties found in the different cultures do not perhaps depend upon the fact that certain of these properties become modified by frequency of transplantation, and whether Albrecht's and Weichselbaum's descriptions do not relate to the first transplantation, and those of Jaeger to cultures several generations older.

In the early days of our researches, we, in common with several other bacteriologists, especially Baumgarten, held to the theory that the Weichselbaum microbe was a degenerated form of the pneumococcus. This view was based on their weak vitality, the difficulty of obtaining cultures, and their very slight pathogenic action. We frankly acknowledge that up to the present time no facts have appeared to justify such supposition, and that there is every reason to believe that the pneumococcus and Weichselbaum's organism are different microbes. But, on the other hand, we cannot indorse the opinion of Jaeger, which is apparently shared by Heubner, Councilman, Albrecht and Ghon, and Jündell, to the effect that the Weichselbaum microbe is the exclusive agent in epidemic cerebrospinal meningitis. Admitting that it alone appeared to be the cause of the epidemics in Berlin, Boston, Copenhagen, Trifail, Stockholm, Dublin, Marseilles, Avignon, Constantine, etc., yet epidemics no less characteristic of meningitis have been caused by the pneumococcus and its epidemic varieties in Turin (Foà and Uffreduzzi), Padua (Bonôme), Sassari (Quaddu), Righi, Lonaconing (Flexner), Carlsruhe (Panienski), and Senegal (Marchoux).

Since the beginning of the small Paris epidemic, we have constantly seen parallel cases due to the pneumococcus and to the organism of Weichselbaum. Out of 44 cases* of primary suppurative meningitis

* We have eliminated from this analysis all cases of secondary meningitis, or those coinciding with other infections, whether local or general, to the number of 15 during the same period; 7 after otitis, 2 following pneumonia, 1 puerperal infection, 1 erysipelas, 1 abscess of the brain, 1 abscess of the shoulder, 1 septicæmia, and 1 influenza. The microbes found in these 15 cases were the streptococcus in 8, the pneumococcus in 5, Pfeiffer's bacillus in 1, and saprophytes in 1.

observed from 1898 to 1901, we found Weichselbaum's organism 23 times; pneumococcus type 10 times; modified pneumococcus (Bonôme) 11 times.

The chronological distribution was as follows:

	Bonôme.	Pneumococcus.	Weichselbaum.
1898	8	1	
1899	2	6	8
1900	1	1	11
1901	..	2	4

It will be seen that in the beginning of the epidemic the pneumococcus and the Bonôme microbe were the most numerous, that the Weichselbaum microbe appeared later, and that even then there were cases of meningitis which there was no reason to regard as independent of the epidemic and which were caused by another organism.* This coincidence is not limited in its application to the Paris epidemic only. In Marseilles in 1900–1901, cases of meningitis with pneumococci were found at the same time as those with Weichselbaum's coccus. In Hamburg, where cerebrospinal meningitis has raged for several years, we find every year cases of meningitis with pneumococci as well as those with the Weichselbaum microbe. Jündell has observed the same coincidence in Stockholm. We could give many other examples. It is therefore possible to affirm not only the existence of epidemics of cerebrospinal meningitis with pneumococci and with the micrococcus of Weichselbaum, but also the coexistence in the same epidemic of cases caused by one or the other of these microbes. These data are sufficiently bewildering, and matters would be much simplified if a relationship could be proved between the two organisms. From a bacteriological standpoint, however, we are obliged to admit that the species differ. Still another hypothesis presents itself, one which has been suggested by Hünermann, namely, that the true microbe of epidemic meningitis is as yet undiscovered. The presence of the pneumococcus and of Weichselbaum's microbe would, according to this theory, be merely secondary, these organisms which are normally present in the mouth and in the nasal fossæ appearing later merely as they do in the complications of grippe. This hypothesis is not based upon facts. Neither the rod-shaped organism isolated by Hünermann in one of his patients nor the bacillus of Stadelman fulfils the required conditions; and the reasoning used to prove that the pneumococcus and the Weichselbaum organism are capable of causing epidemic meningitis seems to us to be well founded. Possibly we should attribute an important rôle to external influences, whether meteorological or otherwise, which

*This in answer to a remark by Jaeger that in the beginning we may have failed to recognize the Weichselbaum organism from not knowing how to cultivate it.

might favor the multiplication and the virulence of the two different microbes. Epidemiological researches, as we have shown in our article, demonstrate the close relationship between pneumonia and cerebrospinal meningitis. To the examples already quoted we would add a recent one of Schaeffler, who observed, in three out of five places in Hesse, that the epidemic of meningitis was preceded by an epidemic of pneumonia which lasted three weeks.

Contagion.

As a rule, meningitis attacks only one member of a family, or of a house, so that the contagious nature of the disease runs the risk of being unrecognized. To accompany the very convincing observations which we have already reported, we borrow some of Looft, which he found in the statistics of the Norwegian health board. In the district of Nordre Bergenhus a fisherman returned from Noordland suffering from this disease. Three other persons in the house with him contracted the same affection, and a neighbor who had taken care of them also fell ill with it. We will further quote the history of the Wagner family given by Osler. 1. A youth of about twenty years returned home on the 7th of February, 1898, complaining of atrocious pain in the head. He had fever and vomiting, and the neck was curved backward. He was very delirious. The case became rapidly aggravated, and the patient died on Saturday the 12th. 2. A sister who nursed him was taken with similar symptoms on February 14th, and died in four days. 3. A second sister was attacked a few days later, and was considered to be in a desperate condition for fifteen days; improvement then began and recovery followed. 4. The mother, who had nursed all the children, was taken ill on the 17th of March and died in two days. 5. A second boy was admitted to the hospital on the 12th of May. The disease began eight weeks before, and the physician who had attended all the family found cerebrospinal meningitis. He appeared prostrated and for several days was unconscious. He was delirious and imagined that he saw his mother and sisters around his bed. There was no longer any fever or stiffness; the optic nerves were normal. His condition gradually improved, and he left the hospital completely cured on the 10th of June.

Bolton Corney has published the history of an epidemic of meningitis in the Fiji Islands. This archipelago, as we know, includes a large number of islands more or less separated from each other and consequently furnishing a good field for the study of an epidemic. Two only of the islands, Mango and the large island of Viti Leon, were the seat of the epidemic, which almost exclusively attacked the workmen who come every year to about the number of nine thousand

from the New Hebrides and New Britain. These workmen are employed in the numerous sugar-cane plantations, and before and after their engagement they are quartered in stations where they are fairly well isolated. Although the station of Suva was a focus of considerable diffusion, the workmen in the other islands were not attacked. The following case is one of the most demonstrative: Three hundred and twenty-nine immigrants were at work on a sugar-cane plantation in an island named Kanathia about ten miles from Mango. In June, 1887, some of these men were transported to Mango. A few days later three of them were taken with cerebrospinal meningitis in Mango and died. Those who remained in Kanathia were unharmed. Another immigrant left Kanathia in May and went to the station at Suva. He was taken with meningitis on August 24th, at a time when the disease was raging in this place. Another group of immigrants left the station of Kanathia during the month of June and reached Mango. Eight of them in succession were taken with meningitis.

Following Medin, Weigert, and Strümpell, I have held that in meningitis the pathogenic agent penetrates into the meninges by means of the rather easy pathways of communication between the nasal fossæ and the base of the cranium (cribriform plate of the ethmoid). Busquet maintains that he has decisively proved the truth of this view experimentally. In three series of experiments he has succeeded in infecting guinea-pigs and rabbits by introducing into the nasal fossæ a small probe carrying nasal mucus taken from persons suffering with the disease or from convalescents, or cerebrospinal fluid collected at autopsy. In a space of time, varying from one to three days, the animals presented morbid symptoms—fever, general fatigue, prostration, torpor, rapid and marked emaciation, and diarrhœa. One of them, on the thirty-fifth day, was attacked with paralysis of the left leg. Five of the animals died. The cephalorachidian fluid in these five was found to be a little above the normal in amount and usually clear. The meninges, especially at the base of the brain, were found to be congested. The meningococcus was isolated from the cephalorachidian fluid and from the pleura.

Busquet determined the infection and death of animals by inoculating them with the nasal mucus of guinea-pigs infected from human beings. His experiments are most interesting.

Symptoms.

Herrick, Osler, Wilson, Bradwell, Dieulafoy, d'Astros, and others have confirmed our remarks on the importance of Kernig's sign in the diagnosis. It is, however, not to be denied that this sign has been present in cases of pneumonia and typhoid fever without any trace of

meningeal inflammation having been found either by lumbar puncture or at the autopsy. These were probably meningeal forms whose anatomical substratum has not as yet been completely determined. We have demonstrated the fact that the cases of typhoid fever, in the course of which Kernig's sign appears, are of the gravest nature, giving the largest proportion of deaths and of relapses.

The value of lumbar puncture in diagnosis is now generally admitted, and no one hesitates to make use of it. Widal, Sicard, and Ravat emphasize the interest attached to a cytological examination of the fluid extracted by puncture and centrifugated. In cerebrospinal meningitis the proportion of multinuclear leucocytes is markedly increased, while in tuberculous meningitis lymphocytes almost exclusively prevail.

We would, however, remark that the data furnished by this cytological study are by no means so convincing as has been claimed. In the first place, leucocytosis is found in chronic diseases of the nervous system (tabes, general paralysis, multiple sclerosis, cerebrospinal syphilis), as well as in acute meningitis. Moreover, if the examination be made late in the course of a cerebrospinal meningitis, lymphocytes only will be found, the multinuclear cells all having disappeared. Finally, multinuclear leucocytes have been found in large numbers in some cases of tuberculous meningitis. Cytodiagnosis is therefore not infallible. Personally we believe that a macroscopic examination of the clot formed in the fluid obtained by puncture gives nearly as valuable information. In cerebrospinal meningitis this clot is of a yellowish color, and is soft in consistency, so that it can easily be spread out on a slide. In tuberculous meningitis it is white and resistant, being spread out with difficulty.

Widal and Sicard have shown that in cases of tuberculous meningitis iodine appears in the cerebrospinal fluid soon after the ingestion of iodide of potassium. Griffon confirmed this fact and further found that it did not occur in two patients suffering from cerebrospinal meningitis. The non-permeability of the meninges to iodine might therefore be a sign of value in the diagnosis of the nature of the meningitis.

Lumbar puncture repeated at intervals during the course of the disease may to a certain extent keep us informed as to its progress. Thus in a case of meningitis progressing regularly toward recovery, the amount of the purulent deposit becomes less and less, and the microbes diminish in number and are more difficult to secure by cultures. Exacerbation of the disease, on the other hand, is shown by a return of purulence, etc.

These suggestions cannot, however, be made into rules, nor can we invariably regard a meningitis in which the exudate is particularly

rich in pus cells as necessarily fatal. We have seen such cases recover completely and with rather marked rapidity.

Our reservations in regard to the presence of microbes in the nasal mucus have been recognized as well founded by the majority of authors. Schiff found Weichselbaum's organism in the nasal mucus of healthy subjects. Jündell, Albrecht, and Ghon have shown that in certain cases of bronchitis we can find in the bronchial mucus a microbe disposed like coffee grains and very similar to the Weichselbaum micrococcus. This was probably Pfeiffer's catarrhal micrococcus. The same observations can be made in regard to the appearance of the diplococcus in the absence of meningitis in purulent conjunctivitis (Haglund, Carl Fraenkel).

Forms.—We have called attention to abortive and to anomalous forms of cerebrospinal meningitis. The generalized use of lumbar puncture has enabled us to recognize an increasingly large number of cases of the kind of which M. Sicard has made an interesting study under the title of the ambulatory variety of bacterial meningitis. Lannois and Camus lay stress on the rapid defervescence on the ninth day of certain forms of meningitis in adolescents. Unfortunately it was not possible to perform lumbar puncture on any of their three patients.

Cerebrospinal Meningitis and Infantile Paralysis.—The macroscopic and microsopic anatomical changes are not limited to the meninges, and the symptoms noted during the course of cerebrospinal meningitis often indicate a more or less extensive implication of the cerebrospinal axis or of the nerves. It will easily be understood that in certain cases the meningeal symptoms are transitory, giving place to those due to a lesion of the brain or spinal cord. We may even be justified in holding that the pathogenic agents of meningitis may primarily and independently invade certain portions of the cord or of the brain, and this brings up the question of the relation between cerebrospinal meningitis and infantile paralyses, whether cerebral or spinal, and polyneuritis—maladies which are infectious in their nature and which, as we know, sometimes appear to be epidemic. An observation of Schultze made in 1898 squarely faces the question. A child of five years was brought to the clinic with the symptoms of meningitis, which rapidly diminished and gave way to those of acute anterior poliomyelitis. Lumbar puncture performed on the thirteenth day showed coffee-grain organisms resembling the gonococcus and which were incapable of cultivation. The author compared the microbe to that of Weichselbaum.

We have already reported the case of a child who, after having had a cerebrospinal meningitis with very attenuated symptoms, had hemiplegia with aphasia, and in which the fluid obtained by puncture

was found to contain Bonôme's organism. In other of our cases the meningitis has been followed by polyneuritis. In the cases just cited the syndromes followed each other in the same individual, but we have seen a case of cerebrospinal meningitis in a mother followed by polyneuritis in the daughter who had nursed her. Looft noticed simultaneously in Bergen and its outskirts a number of cases of meningitis and of infantile paralysis and polioencephalitis. Similar occurrences have been noticed in America and in England.

Simple Posterior Basal Meningitis of Infants.—Gee and Barlow in 1878 and more recently Carr in 1898, and Still, 1898, have described under the name of "cervical opisthotonos of infants," and "simple posterior basal meningitis of infants" a special meningitis of subacute course, in which the essential symptoms are stiffness and retraction of the neck, opisthotonos, and frequently blindness. This form of meningitis differs from the tuberculous in being curable.

In this form, Still has isolated a microorganism which possesses characteristics very similar to those of the Weichselbaum organism. Hunter and Nuthall in 1901 reported the result of the bacteriological examination of the fluid obtained by lumbar puncture. In seven of the observations the microbe was absolutely identical with the one described by Weichselbaum, while in three other cases it resembled the description given by Jaeger and Heubner (coloring persisting by Gram's method, and abundant development on agar and on potato). There is every reason to regard these cases as being cerebrospinal meningitis, or, to use the expression of Hunter and Nuthall, as a "sporadic manifestation of cerebrospinal meningitis."

Treatment.

Since the original article was written I have had occasion to treat a rather large number of cases of cerebrospinal meningitis, and can merely reaffirm the statements in regard to the value of prolonged hot baths. These baths are usually repeated four or five times a day, the immersion being prolonged from a half to three-quarters of an hour. This method will be seen to differ from that of Aufrecht who gave only one bath daily, and from that of Barr who prolonged the immersion during eleven days and longer.

Formerly I regarded lumbar puncture in this disease as of diagnostic value only. At the present time, however, I consider it a useful means of treatment. It not merely diminishes tension, but also withdraws a considerable number of pathogenic agents and thus increases the powers of defence of the organism. Puncture should be repeated at more or less close intervals during the course of a meningitis. The progress of the disease, the appearance or the reappearance

of new symptoms (rise of temperature, change in the pulse, vomiting) will determine the necessity for puncture. In such a case lumbar puncture has no dangers, providing we are careful not to aspirate so strongly as to remove the natural pressure too suddenly. To avoid this sudden change we no longer puncture with the patient seated, but have him lying on his side. Occasionally the pus is so thick and viscid that it will not flow through the Pravaz syringe. In such a case it has been found well to push a little sterilized air through the lumen of the needle. This enables one to draw out large quantities of pus, and the patient recovers without it having been found necessary to perform laminectomy.

Various opinions are held in regard to the value of lumbar puncture. Williams claims to have obtained immediate and marked relief by its use. Wentworth and Osler are less enthusiastic. The immediate effects corresponding to relief of pressure have been observed under many circumstances. As a rule, restlessness is diminished; the patient may even go to sleep during the operation and remain asleep some time. The momentary disappearance of Kernig's sign has been observed in a number of cases, and evidently bears witness to a favorable change.

The great use of lumbar puncture in suppurative meningitis appears to consist in the fact that a large number of the pathogenic agents are removed and that ventricular dropsy which might lead to hydrocephalus is prevented.

TETANUS.

BY

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BUCHAREST.

DURING the last three years numerous works have been published on tetanus which have been confined chiefly to a consideration of tetanus toxin and antitoxin. Especially is this true since the appearance of Ehrlich's very suggestive theory with respect to the manner of action of these substances. The treatment of the disease has, however, been but little advanced by these studies, and the newer methods and recommendations have not given materially better results than were formerly obtained; but our knowledge of the pathology has been considerably increased.

Etiology.

While Vaillard, Vincent, and Roger have claimed that tetanus is produced only as the result of bacterial association, Strick has shown that pure cultures of tetanus spores can produce the disease if the tissues are previously prepared for their reception. Especially favorable lesions are gunshot wounds and hæmatoma, together with various experimental wounds produced in animals. Indeed simple intramuscular inoculations of tetanus spores, toxin-free, usually fail to produce tetanus, while a similar infection of hæmatomata or gunshot wounds regularly gives rise to the disease. However, the animals infected in this manner could be completely protected by the prophylactic or therapeutic use of a powerful antiserum in sufficient quantity (20 c.c. of the Bern serum for every 1 to 1,000,000,000 part of the weight of the animal). These researches have also recently shown that rabbits are easily cured of tetanus by the use of antitoxin.

Latterly the enumeration of the auxiliary causes of human tetanus has uncommonly increased. Thus are recorded several cases of gingivitis followed by tetanus in which the latter disease disappeared upon extraction of the teeth. Also several cases have been described by Favre in which tetanus followed an operation for paraphimosis, and another in which the disease followed slight traumatism of the testicles. In the latter it is remarkable that the tetanus symptoms first appeared

two to four days after the occurrence of the trauma. In these cases the use of antitoxin and other means within a few days after the appearance of the symptoms was without avail in preventing the fatal termination. The numerous cases of puerperal tetanus which have recently been observed have run a severe course and have not been influenced by the employment of antitoxin. In accordance with the results of my researches I believe that these cases of puerperal tetanus are caused by an infection of the uterine placental surface with tetanus spores transported in supposedly sterilized fluids used as intrauterine injections. Nevertheless many of these cases show previous infection with other microorganisms. This, however, is far from being always the case.

In the last few years many endeavors have been made to produce tetanus without local injury. Carrière has shown that tetanus toxin is not absorbed from the digestive tract, being destroyed by the ptyalin, gastric juice, bile, or pancreatic secretion. Subsequently Thalmann found that a catarrhal condition of the pharyngeal or nasal mucous membrane rendered infection with tetanus spores possible, and that slight injuries of these structures were especially favorable for the production of tetanus by inhalation. In all probability so-called idiopathic tetanus and rheumatic tetanus arise in this manner. This author also describes fatal cases without tetanic spasms following the inoculation of wounds with tetanus spores.

Recently numerous cases have been observed in which tetanic symptoms, usually slight in nature, have appeared following or during the course of infectious diseases, intestinal intussusception without injury, and operations for the same. Such cases have been at times described as "tetanoid," while other observers have considered them to be true tetanus. Thus a case of tetanus, which was cured by antitoxin, has been reported following a bodily injury accompanied by severe compression of the intestines. Veihr has recorded a case of tetanus of six weeks' duration accompanying scarlet fever. Here the muscular contractions were not continuous but were present only during rest and involved the various voluntary muscle groups. It is an interesting fact that in this case no fever was present during the course of the primary disease. Still another case of tetanus has been observed following a successful gastroenterostomy for stricture of the pylorus. Here the tetanic symptoms appeared as the apparent result of percussion of the stomach. The case had previously been treated by dilatation methods. The tetanus ran a fatal course.

Bacteriology.

Several important practical questions with regard to the tetanus bacillus have been submitted to extended research during the past few years. With respect to the resistance of the bacilli in the dead ani-

mal body Rohard found that live tetanus organisms were present after thirteen days at the site of inoculation in guinea-pigs and mice which had been infected with tetanus spores and kept in glass receptacles at 5° C. This fact is of forensic value, as after the interment of those dead from tetanus the microorganisms contaminate the tissues of the cadaver from both the local lesion and the intestinal canal. In fact, I have recently convinced myself of the presence of tetanus organisms in the intestinal canal of both men and animals.

Putrefaction has an especially favorable action on the growth and metabolic process of tetanus organisms. Schütze has shown that the inoculation of putrefactive products increases the action of these organisms. The same predisposes to the outbreak of a very rapid and malignant form of tetanus. Even attenuated tetanus germs are able to regain their virulence when placed in the presence of such products.

In spite of the fact that the bacillus in its local situation gives rise to products which are diffused throughout the system, these microorganisms reach the neighboring lymphatic glands by way of the lymph channels, and it is also possible for them to pass directly into the blood. Bacterial association is especially favorable for the diffusion of the organisms throughout the body in this manner. Furthermore, tetanus bacilli in very severe infections have been frequently found in the internal organs. Oettingen and Zumpe in forty-five infected animals found the bacilli in the internal organs twenty times.

Various authors have found pseudotetanus bacilli on wound surfaces or in the intestinal canal; thus Tavel found them in an intestinal abscess. These bacilli possess morphological and cultural characteristics very similar to those of genuine tetanus organisms. They are not, however, pathogenic. From the fact that I have often convinced myself that under certain conditions the tetanus bacillus very easily loses its pathogenic properties, it is quite probable that under favorable circumstances these so-called pseudobacilli may become virulent. When these organisms become attenuated the spores appear smaller and the morphology of the microorganisms very closely approaches that of tetanus-like intestinal bacteria from which it is very difficult to differentiate them. This frequently takes place when the bacilli are sufficiently exposed to the air.

Tetanus Toxin.

In the serum therapy of tetanus great importance attaches to the manner in which the toxin is diffused in the animal body and the mode of its excretion. Recent researches have shown that the toxin is present in the different internal organs. This is certainly true with

respect to the central nervous system. Marie has shown that the greater the quantity and strength of the inoculated toxin and the slower its absorption, the longer time it can be demonstrated in the body. Thus after intravenous inoculations it vanishes very quickly, and the same occurs after intracranial inoculations. I have found the toxin in the secretions only exceptionally and then solely after the inoculation of large quantities. After the repeated inoculations of large quantities of toxin the amount present in the secretions is but little increased, so that it must be conceived that soon after introduction into the body the toxin is anchored in the central nervous system. It is questionable, however, whether the toxin itself enters into this union or whether that is brought about by the presence of another substance produced by the body as the result of the action of the toxin. The results of my researches favor the latter conception, since I have found that the presence of the toxin in the body cannot be demonstrated previous to the appearance of the clinical symptoms of the disease. Also the incubation of the disease after the toxin inoculation lends strength to this view.

The theory of the mode of action of the toxin has been extensively studied during the past few years. Metchnikoff showed that if the brain of a normal guinea-pig, which is not resistant to the toxin, is rubbed up and mixed with the toxin, such a mixture is able to protect at least ten guinea-pigs against tetanus infection. Metchnikoff believes that this brain-toxin mixture, when introduced into the animal body, occasions a leucocytosis, which latter destroys the toxin. This view is, however, not conceivable because after natural tetanus infection marked leucocytosis occurs in the infected region, but this has no effect in subduing the symptoms of the disease. Ehrlich's theory explains the apparent contradiction between the action of living and that of dead brain substance. Both of these substances anchor the toxin. In the living brain this leads to a destruction of the nerve cells and death before such cells are saturated with the toxin, while in dead brain a large quantity of the toxin can be taken up by the nerve cells, which naturally forms a powerful protection against the injury of other living nerve cells. The fact that the brain substance of tetanized or naturally immune animals forms little or no toxin, although there is also here a leucocytosis, further contradicts Metchnikoff's view. Toxin is not present in such a mixture because in a tetanus brain the nerve cells are already provided with toxin and because in naturally immune animals the nerve cells possess little affinity for the toxin, upon which fact depends, in a great measure, the natural immunity. Marie's researches are of value only in so far as they show that different portions of the brain protect against tetanus in a different degree, the superficial portions giving the greatest pro-

tection. According to my researches the medulla oblongata also possesses this property in a marked degree. If an animal is inoculated at the same time with both brain substance and toxin, these substances being introduced into separate locations far removed from each other, death from tetanus regularly follows. For this reason Marie contested Wassermann's theory that the brain substance acts as an antitoxin. Marie's experiments, however, prove nothing against this idea. Antitoxin is a serum in which the receptors are present in a very finely divided molecular form and for this reason are quickly disseminated throughout the system by means of the circulation, while in normal brain substance the receptors are united to the nerve cells, which makes them naturally much less easily diffusable than is the case with antitoxin, so that they do not come in contact with the toxin when they are inoculated at a site remote from its location. From these considerations the mode of action of normal brain substance upon tetanus toxin is made perfectly clear. The researches of Ransom are of interest. He has shown that the internal administration of tetanus toxin is not harmful, and that the toxin is not influenced by the process of digestion but passes through the intestine unchanged.

Different observers have endeavored to account for the long incubation period of tetanus. The same is present after experimental toxin inoculations, and the development of symptoms in natural tetanus evidently does not correspond with the time of the toxin formation at the site of the infection. It can be conceived that the toxin may gain admittance to the nerve cells and even be anchored therein without becoming active until some special cause is operative. On the other hand it has been shown that direct intracranial inoculation of toxin materially shortens the incubation period. In a similar manner the incubation is shortened if the organ extracts of tetanized animals are used for inoculation. In such cases it is to be supposed that the inoculated organ extracts contained toxins produced by the combination of the organ cells and the toxin and that no incubation is necessary for its action (Tauber). Stinzing has found that the clinical symptoms appear very soon after the subcutaneous inoculation of the spinal fluid of tetanized animals. These researches show that the tetanus poison is not taken up as such by the nerve cells but is changed in the organism, and that this preparation requires a certain time which corresponds to the incubation period of the disease.

Recent researches have shown that in addition to the tetanus toxin other substances are produced by the bacillus or arise from the action of the tissues upon such products, which exercise a certain effect upon the body. Ehrlich and Madsen have shown that in addition to tetanus spasmin, tetanus lysin is present and is to be considered the convulsion-producing poison. These two poisonous substances are pres-

ent in different proportions in various toxins. The lysin is the less resistant to heat. Spasmin can be obtained alone if red blood cells are added to the toxin. These enter into combination with the lysin. Antilysin can be produced by the inoculation of lysin. If one mixes in a test tube red blood cells and tetanus lysin, this poison enters into the erythrocytes and after a time dissolves or destroys them. If during this process tetanus antilysin is added to the mixture, the antilysin is able to extract the lysin from the red cells. It has, however, been shown that in man the antispastic toxin is not able to extract the anchored poison from the erythrocytes. Tetanus lysin, moreover, appears to be a complex body, just as diphtheria toxin by partial saturation can be broken up into a number of components. If these components are considered under two classes, we find that they should be classified first as very toxic and second as slightly toxic. In the first class three groups can be differentiated—prototoxin, deuterotoxin, and tritotoxin. The prototoxin constitutes only one-thirteenth of the entire toxin, but is the most important constituent since one-half of the hæmolytic power of the toxin is due to the presence of this substance. It is very unstable and easily passes into a toxoid, in that its haptophore group remains unaltered while its toxophore group loses its power. Deuterotoxin constitutes one-ninth of the entire toxin. It is less powerful but more stable than the prototoxin. Tritotoxin is very weak and entirely loses its power when kept in temperatures below 10° C. The second half of the toxin, as has been said, is very slightly toxic, and can be designated as toxon. However, this poison, which differs from diphtheria toxin in that it produces hæmolysis, but often requires the addition of a complement therefor, should be further examined in order to ascertain whether it contains amboceptors and complements. The above properties of tetanus toxin justify the opinion that this poison is not analogous in its composition to diphtheria toxin.

Pathological Anatomy.

The microscopical lesions of the central nervous system in tetanus have been subjected to extensive study. According to Ehrlich's theory, the toxin acts directly upon the large motor nerve cells, and one should naturally expect to find marked changes in these structures. However, most of the lesions found are of a secondary nature. Claude has described disseminated inflammatory centres in the bone marrow of a dog which as the result of infection with tetanus toxin showed diplegia. Prolonged cases show more extensive lesions than acute cases; in such cell infiltration is marked in and around the nerve cells. My observations show that in time the altered nerve cells produce an exudative inflammation around the blood-vessels.

Courmont, Doyon, and Paviot have recently as the result of their studies laid special stress upon the alterations observed in the nerve cells. As is well known, Marinescu claims to have found specific alterations (hemorrhages and chromatolysis) in tetanus. I have, however, been able to find no uniform alterations in this disease. The first-named authors hold that the histological changes in the nerve cells do not explain the muscular convulsions present in tetanus, since such changes are found diffused over the entire brain and are not limited to the tetanic zone; and furthermore, that such changes are often found in healthy guinea-pigs while they are frequently absent in these animals dead of tetanus; and finally that these changes are usually absent in animals with but slightly susceptible nerve cells, such as dogs. These authors also maintain that the characteristic changes described by Marinescu are usually not present in this disease. Numerous other authors, as Goldscheider, Flatau, Hunter, and Blumenthal, are of the same opinion. Joukowsky has described in tetanus a diffuse increase of wandering cells in the gray matter. Similar observations have been made and especially emphasized by me for some time past. Courmont, Doyon, and Paviot have met with identical appearances in experimental tetanus in a horse in which the surface of the brain showed numerous patches of cell infiltration. I have some time since shown that the lesions in rabies and tetanus differ in so far that in the former disease the regional changes in the brain correspond to the clinical symptoms in a large measure, while in tetanus the changes are much more diffused over the brain, especially in chronic cases. For this reason we are bound to assume that hitherto the important changes in the tetanic zone in tetanus have escaped our observation. However, a swelling of the nucleoli of the nerve cells, often with an extrusion of the same from the nucleus, and an enlargement of Nissl's cell bodies have been observed by Tauber and Westphal, and have been especially emphasized by Goldscheider and Flatau. More prominent lesions are a central myelitis of the dorsal portion of the cord with destruction of the large pyramidal cells in the anterior horns. These have been accurately described by Donnetti. Stinzing found in a similar location hemorrhage, marked degeneration, and destruction of the cells in the anterior horns, with dissolution of Nissl's bodies and of the cell nuclei. All these observations show that in tetanus a great number of pathological lesions may be present which explain only in part the symptomatology of the disease. I accept Ehrlich's theory that there must be present in the large nerve cells of the tetanic zone peculiar segmentary changes similar in character to those which I have found in some cases in the central cells of the spinal cord.

Symptomatology.

The important question as to why the convulsions first appear in animals in the region of the infecting lesion while in man the jaws are primarily affected, has not been as yet explained. Stinzing believes that this is due to the size of the lymph channels in man, and that in animals in consequence of the narrow lymph channels the toxin is concentrated and retained in close proximity to the nerves of the infected region, and hence convulsions are first present in this location. This does not appear to me to be a valid explanation, since in large animals with spacious lymph channels a like primary appearance of convulsions in the infected region is observed. I think that a more probable explanation is to be found in the fact that in animals reflex nervous manifestations are less easily produced than in man, in whom highly ordered nerve centres predispose to reflex phenomena.

The temperature elevations in tetanus correspond to the virulence of the toxin and the susceptibility and age of the animal. Thus Courmont and Pehn have found that after the appearance and generalization of the convulsions some animals show subnormal while others show hypernormal temperatures. In the latter case the temperature may still continue to rise after death. In men, horses, goats, and dogs the disease is accompanied by fever, while in mice, guinea-pigs, rabbits, and fowls subnormal temperatures are present. Dogs, hens, and young goats usually show hypothermia, while pups show hyperthermia. Perhaps this may also vary with the size of the animal.

For a long time peculiar cases of tetanus have been observed in which, following infection, cachectic appearances and eventually death occur without the development of tetanic symptoms. Dönitz has designated these cases as examples of *tetanus sine tetano*, which he has produced in rabbits by the intravenous inoculation of small quantities of toxin or of toxin mixed with antitoxin. According to Ehrlich and Migoimito the explanation of these cases is not to be sought in the presence of tetanus lysin or in the hæmolysis, but in the supposition that the entire toxin is anchored in other cells than those of the central nervous system. However, Dönitz has also shown that hæmolysis is not the causative factor since the employed toxin was not hæmolytic. It is probable that in these cases the toxin is changed in some manner so as to bring about the cachectic condition, for we know that such changes may occur in other toxins.

During the past few years many cases of local tetanus have been observed. Adrain reported a case in a hostler with enlarged lymphatic glands in the left cervical region who without previous external injury suddenly developed stiffness of the left side of the neck with left

masseter convulsions and stiffness of the muscles of the lower limbs combined with a marked increase in the reflex and muscular irritability. The man recovered. Alban and Stinzing have observed a similar case of enlargement of the lymphatic glands in which an infection had probably been concealed. Such cases are different from those described by Binot, who produced local manifestations of the disease in guinea-pigs by inoculating the toxin into the uterus, testicles, and kidneys. Here the period of incubation was lengthened, but the course of the disease was very rapid. Especially after inoculations into the diaphragm is the course of the disease very severe. After the inoculation of one-tenth of the fatal dose in this manner it is impossible to save the animal by the use of antitoxin.

Finally cases of tetanus have been described as complicating infectious diseases (scarlet fever) and certain intestinal diseases. These are usually light in nature and recovery takes place as a rule. Such cases are generally described as tetanoid, although in many instances characteristic tetanus convulsions are present.

During the last few years many cases of tetanus have been observed in which various complications have been present at the site of infection. Among such may be mentioned erysipelas, gangrene, necrosis, and combined infection with putrefactive bacteria or their products. The unfavorable influence upon the course of the disease occasioned by the latter complication has been especially emphasized. A widely diffused erythema has been frequently observed following subcutaneous antitoxin inoculations, but no unfavorable influences appear to be caused thereby. Frequently, following such inoculations the general condition of the patient becomes rapidly worse and the muscular rigidity of the inoculated region is increased. Death from abscess of the brain or intracranial hemorrhage has been observed as the result of intracerebral antitoxin inoculations. Such a case has been reported by Gibb in which repeated intracerebral antitoxin inoculations were administered and in which recovery from tetanus took place. Following recovery an abscess developed in the frontal lobes of the brain and death ensued. In a peculiar case of puerperal tetanus a complicating pneumonia appeared which pursued a characteristic course and was followed by complete recovery.

Prophylaxis.

While it cannot be shown that the employment of tetanus antitoxin has yielded satisfactory results in the treatment of the fully developed disease, it has nevertheless been abundantly proven by experimental research that the inoculation of such antitoxin a short time previous to the outbreak of the tetanus symptoms is fully able to save the life

of the animal. Hence the prophylactic subcutaneous inoculation of antitoxin is to be recommended following wounds contaminated with soil, gunshot wounds, extensive traumatic gangrenous injuries, wounds of hostlers and gardeners, and in suspicious cases of labor at full term or in abortions. In such cases 3 gm. of Höchst antitoxin diluted in 30 c.c. of water should be administered. Since this dried antitoxin retains its power for a very long time it should be kept constantly on hand by military and colonial physicians and country obstetricians, and should always be found at accident stations, surgical and obstetrical hospitals and clinics, and at all pharmacies. Nocard has found that the routine employment of prophylactic antitoxin inoculations has materially lessened the frequency of the disease among horses.

Treatment.

Non-Specific Treatment.—In the non-specific treatment of tetanus the employment of *narcotics* takes first rank. The use of these remedies is based upon the fact that in cases of tetanus the symptoms of the disease markedly lessen or entirely vanish during sleep, although the sleep itself may be greatly disturbed. By the use of sulfonal and trional in large doses I have produced sleep and an improvement of the condition, and the same result has followed hypodermic injections of large doses of morphine. However, usually in such cases antitoxin or carbolic acid has also been employed and to these the recoveries may possibly be ascribed. In severe cases narcotics are usually without effect. Babinsky has reported a case of tetanus which occurred in a morphine habitué through infection of the needle wound which was treated with bromoform and very large doses of morphine muriate (gr. 5½—0.35 gm.) and in which recovery took place after four weeks. In animals (guinea-pigs) hypodermics of morphine prolong the course of the disease. Thalmann, as the result of experimental research, recommends the use of protracted oxygen inhalations and expectorants especially in idiopathic and rheumatic tetanus. Constantinescu has reported the successful treatment of a severe case by pilocarpine injections. Theoretically the use of pilocarpine is rational since it favors the production of antitoxin by the body. Other narcotics, such as urethane, have been used. They operate in the same manner as morphine and chloral. Finally the injection of an artificial blood serum has been used after venous bleeding and tolerably good results have been obtained therefrom.

Recently Baccelli's *carbolic-acid* method and also *amputation* have found a number of supporters. I have obtained encouraging results from the employment of the former; also by the use of the antiserum, prepared in Bucharest, and the combined methods. The esti-

mation of the value of the different methods is very difficult, but I do not agree with Ascoli that subcutaneous inoculations of carbolic acid give better results than does serum therapy. Ascoli reports 47 cases of which 10 were treated with Tizzoni's and 33 with Behring's antitoxin; of these 13 resulted fatally. Of 33 treated with carbolic acid there was but 1 death. It is certain that the cases reported by Natoli, Delore, and Benvenuti were light attacks. My experiments with dogs showed good results from the use of carbolic acid, while this substance used upon goats by Tosia was entirely without effect. In drawing comparisons of methods of treatment of a disease in which the mortality is from ninety to one hundred per cent. it is necessary to exclude light cases and those in which the tetanic symptoms do not appear within two weeks following the infection.

The same rules should be applied in estimating the value of amputation, especially in those cases in which the convulsions first appear in the region of the local infection. For this reason the cases reported by Clemmery and Maturie are to be excluded from consideration. This class of cases is most suitable for amputation, but the use of an antiserum or carbolic acid as well as narcotics should not be neglected.

I as well as Ascoli have used large doses of carbolic acid in the treatment of this disease and have never noticed the appearance of poisonous symptoms therefrom. Ascoli recommends injections of 0.72 gm. of a three-per-cent. solution daily for weeks. With such dosage he has never produced poisoning and has never observed albumin in the urine, headache, or intestinal pains. In many cases mixtures of carbolic acid and camphor were used.

Our method of treating infections of the nervous system by the administration of *brain substance*, which was shown by Wassermann to have a scientific foundation, has been frequently employed in tetanus. In a certain sense such methods are specific in nature in that the receptors of the injected nerve cells unite with the tetanus toxin. It has, however, been shown that it is more difficult to protect animals by inoculation of brain substance than by an antiserum. Nevertheless, fair results have been obtained in men by this treatment. In two cases of severe tetanus I have injected the brain substance of sheep; in both recovery took place. There have been eleven cases reported in which this method was used, but the majority of them were not severe. In all there were only three of these fatal. These cases were treated by the subcutaneous inoculation of emulsified calves' or rabbits' brains, antiseptic precautions being observed. I would especially recommend, when this method is employed, that the brains of very susceptible animals be used, and particularly those portions in which the large motor cells are present.

Specific Treatment.—In the serum therapy of tetanus a question of the highest importance is whether the toxin lodged in the nerve cells can be withdrawn from the same by the antitoxin. This largely depends upon the manner in which the toxin is united to such nerve cells. We must conceive that in tetanus, in addition to the specific toxin and its combination with the nerve cells, other less specific toxins are at work whose action cannot be influenced by a withdrawal of the specific toxin from the nerve cells. Thus in the tetanus of rabbits, in addition to the characteristic tetanic symptoms, a general cachexia appears, showing that the poison is quickly absorbed into the blood. Dönitz especially has shown that antitoxin is able to release the toxin from its combination with the tissues, especially in the beginning of the disease. I believe that in such cases the toxin is not at all or only in small portion in combination with the nerve cells, but is principally lodged in elements less important to life, and that it enters into a less stable combination with such elements than it does with the nerve cells. Also in men many of the most dangerous symptoms are not to be ascribed to the combination of the toxin with the nerve cells, and it must be conceived that also here the toxin gradually enters into combination with such cells. Only in this manner can be explained the fact that antitoxin is relatively more efficacious at the beginning of the disease when few nerve cells are affected, and it seems certain that after the toxin has become lodged in the nerve cells it cannot be extracted therefrom by antitoxin. It is also certain that the nerve cells of different animals vary in their power firmly to retain the toxin. Thus the nerve cells of rabbits, mice, and rats give up the tetanus toxin lodged in them more easily than do the nerve cells of man. Serum therapy therefore gives more favorable results in these animals than it does in man.

The researches of Roux and Borell temporarily raised the hope hat the dural injection of antitoxin might be more efficacious than the subcutaneous in the treatment of the disease in man and might uniformly cure the disease. My researches and those of Blumenthal, however, have shown that such is not the case, for even in very light cases with the employment of this method we obtained unfavorable results. Blumenthal also has shown that in goats the subdural inoculation of antitoxin, even in the first stages of the disease, in no way produces a favorable result.

The numerous cases which have been reported as treated with antitetanic serum have shown but a trifling reduction in the mortality thereby. And this is the case even in those cases in which the antitoxin was used in large doses and within two days after the appearance of the clinical symptoms. Köhler's statistics of 96 cases show no apparent favorable action of the antiserum, and even in 31 cases in

which the serum was used within two days after the clinical symptoms appeared the mortality was 64.05 per cent.

In spite of the unfavorable results obtained in tetanus by the use of antitoxin, Behring has endeavored to establish the value of his serum. He prepared, by the addition of malachite green, sodium phosphate, and toluol, a stable tetanus toxin. Tizzoni, whose antiserum is regarded as non-effective by Behring, claims that his tetanus bacilli differ from Behring's in that they produce no stable toxin. Behring as the result of later researches denies this. Tizzoni ascribes the superior results obtained by Behring to the character of the cases treated and the time of the inoculations. However, there is no doubt but that Behring's antiserum gives better results than Tizzoni's. Both Behring and Tizzoni agree that the inoculation should be made in close proximity to the local infecting lesion, and that at first not more than 20 c.c. (200 antitoxin units) should be used. We have seen that intracranial and intravenous inoculations of antitoxin give poor results. For this reason Leyden has recently used intrarachidian inoculation and has obtained fairly good results. However, the cases so treated by him were mild, and an opinion of this method must be at present withheld. It is nevertheless easier of execution than the intracranial which involves trephination. Blumenthal's experimental researches with this method have given unfavorable results. He inoculated animals by lumbar puncture immediately after the first appearance of the tetanic symptoms with two thousand times the quantity of antiserum necessary to neutralize in a test tube the amount of toxin injected. In no case was the life of the animal saved. His experiments were conducted upon goats, and it is hence certain that in these animals the toxin from the beginning is so firmly united with the nerve cells that it cannot be extracted therefrom by the antitoxin.

The statistics gathered by me in regard to the results obtained by the use of antiserum in human tetanus are fairly trustworthy. They do not correspond with Behring's assertion that the mortality is reduced 15.7 per cent. in cases in which the inoculation of at least 100 antitoxin units is instituted within thirty hours after the appearance of the symptoms. It appears, however, that in mild and moderately severe cases somewhat better results have been obtained than by the use of non-specific methods, and that perhaps recovery is more rapid. In severe cases no better results have been obtained. Other authors have collected much more favorable statistics. Thus Moschowitz has collected 290 cases in which an antiserum was used and the mortality was 40 per cent. Among these were 33 severe cases of which 19 (?) ended in recovery. Of 41 cases treated by intracranial inoculations 57 per cent. terminated fatally.

Puerperal tetanus gives an especially bad prognosis. Kentmann

has collected 45 cases; 30 were of labor at full term, 4 were of miscarriage, and 11 of abortion. All cases showed clinical symptoms. In 16 of these cases antitoxin was used immediately after the appearance of the first symptoms. Only one case ended in recovery, and this ran a chronic course. Behring recommends in general that the inoculations be made near the local infecting lesion and in cases of puerperal tetanus into the inner surface of the uterine wall. Recently a few severe cases of puerperal tetanus have been reported in which recovery has taken place after lumbar inoculations.

My own experience with the antiserum prepared at the Bucharest Institute has been relatively favorable. Twelve patients have been inoculated; of these only two died. Both of these were severe cases and one of them was puerperal. Among the patients who recovered were three in which the incubation was less than seven days, and four in which it was less than two weeks. In four cases the convulsions were general from the beginning. In these cases 300 toxin units were inoculated within thirty hours after the onset of symptoms. In two cases lumbar puncture was used. Usually there appeared an improvement in the symptoms after the first inoculation, but this did not always continue. In three cases carbolic injections of 0.5 c.c. daily were also given.

It is always necessary to employ other means in addition to the antitoxin inoculations. First in importance is the removal of all foreign bodies from the wound and its thorough cleansing with bichloride, which energetically destroys the bacillus. A bichloride dressing should also be applied. Narcotics should also be given in large doses. The best results in severe cases are to be obtained only in the conjoined use of such measures.

A review of these 119 cases, which I have collected and tabulated, shows that 42 ended in recovery, of which 2 received no antiserum. The mortality of the disease with the administration of antitoxin is therefore 70 per cent. Among the cases which ended in recovery only one or two are described as severe. Several are described as severe, but the history shows that they were light or at the most moderately severe cases, and it is well known that many of these end in recovery without antiserum treatment. It can, however, be said that moderately severe and light cases terminate favorably more quickly when antitoxin is given than when it is withheld. Poor results followed the use of intracranial inoculations. All the severe cases ended fatally, and antitoxin inoculations very soon after the appearance of the symptoms were without avail. Many authors hold that the mortality is greater when early inoculations are resorted to than when these are delayed. In the statistics which I have collected it is shown that those cases which ended in recovery were in general inoculated later than

those which terminated fatally. It is also shown that the inoculations are not always followed by an immediate improvement in the symptoms in either fatal or non-fatal cases.

We are therefore under no illusion when we state that antiserum inoculations, as they are used to-day in the treatment of tetanus, give very unsatisfactory results. Indeed inoculations of carbolic acid and brain substance give better results than does the specific treatment. It appears to me probable that a satisfactory specific treatment for tetanus will yet be found, and I believe that this will be obtained by improving the antiserum and its method of use. In order not to raise vain hopes and to encourage further research and investigation, it is necessary to emphasize the fact that antiserum as used to-day is of but slight utility in mild cases and practically worthless in severe cases of tetanus.

Immunity.

We have seen that immunity against tetanus depends upon different factors. The chief factor is the susceptibility of the nerve cells to the tetanus toxin. The researches of Blumenthal have shown that those animals are predisposed to tetanus whose nerve cells are rich in substances which unite with tetanus toxin. These are to be called specific receptors. On the other hand, naturally immune animals possess but few such receptors. In fact, the toxin is anchored to the cell substance by these receptors, and in this manner there is produced a chemical change in the cell substance which gives rise to the tetanic symptoms. It is, however, possible that natural immunity depends not so much upon the absence of specific receptors as upon the kind of union formed in the cell between the toxin and the cell body which is dependent upon chemical and morphological properties of the cell protoplasm. That such a factor plays an important part in natural immunity is shown by my researches on frogs and birds which are tolerably immune to tetanus. When I kept frogs at a high temperature they became susceptible to this disease. It is hardly probable that new receptors could have been formed in the nerve cells of the frogs as the result of the increased temperature, but it is much more likely that as the result of this the protoplasm of the nerve cells was so changed that it became susceptible to the toxin. A general weakening of the body produces similar results in naturally immune animals and makes them very susceptible. Artificial immunity has been satisfactorily explained by the side-chain theory and Weigert's amplification of it. It is certain that immunity is produced by the irritation of the toxin which causes an overproduction of receptors or side-chains, which are thrown off from the cell and pass into the circulating blood. These possess both a haptophore and toxophore group,

which unite with the toxin in an entirely similar manner as do the receptors in the nerve cell. The serum of immunized animals possesses a large quantity of such receptors, which when introduced into another animal seize the toxin before it can unite with the nerve cells. However, numerous researches have shown that tetanus toxin is no simple substance, and in consequence it must possess different receptors for different substances. In addition to this, tetanus poison may lose a portion of its toxin and be changed into a toxoid. In this process the haptophore group remains unchanged, but the toxophore group, being less resistant, disappears. This toxoid unites with the receptor in the nerve cell and does not injure the latter, but the receptor is used up in the process and fails to protect the cell against other toxoid molecules. The researches of Behring and Ransom have confirmed this view. Working with constant tetanus toxin solutions they found that a larger quantity of antitoxin produced from a tetanus toxoid was necessary for immunization than when the antitoxin was produced with a virulent tetanus toxin. An experiment of Ransom's in this connection is very interesting. He found that in a dove dead of tetanus all the organs contained the toxin with the exception of the central nervous system, which can be explained only on the supposition that the toxin had united with the nerve cells and had been changed. Although in general Ehrlich's immunization theory appears sound, there exist difficulties in the interpretation of different appearances. There are often present in the bodies of animals infected with toxin different processes which are explained with difficulty by his theory. Thus rabbits can be immunized by the use of toxon without antitoxin being produced. Also guinea-pigs and men who have withstood a tetanus infection and are very resistant contain no antitoxin. On the other hand, many animals such as hens, rats, and alligators, after inoculation with tetanus toxin produce great quantities of antitoxin without previously showing any signs of the disease. How is it to be explained that immunized animals after bleeding produce a large amount of antitoxin in a very short time, or that the administration of pilocarpine markedly increases the production of antitoxin? However, if it is possible to explain all of these appearances as well as many others by Ehrlich's side-chain theory, it is also true that they can be explained in other ways. More difficult of explanation is the fact that the brain of warm frogs or susceptible toads and the spinal cord of hens cannot neutralize the tetanus toxin *in vitro* (Courmont, Doyer, Metchnikoff). Especially hard to explain are the facts that hens are not susceptible to subcutaneous inoculations but extremely susceptible to intracerebral (Behring), and the immunized rabbits succumb after the intracerebral inoculation of small doses of toxin (Roux, Borell). According to my opinion these results show that

immunity is not so simply produced as Ehrlich supposes. *In toto*, however, Ehrlich's theory forms the foundation of our conception of immunizing processes, but the same is capable of much development and amplification. Thus it is very probable that after subcutaneous inoculations a large portion of the tetanus toxin does not reach the nerve cells, but is united to other cells which also possess receptors or can set antitoxin free. Also it can be conceived that throwing off of the receptors by the cells is produced not only by the specific irritation but by other less specific influences. My researches have shown that mixture of antitoxin and toxin, which is not toxic, is able to produce immunity, and it must be conceived that the free haptophore group of the receptors is still able to enter into the nerve cells and combine there with the toxin. Finally we must conceive that antitoxin formation in its entirety is not due solely to a specific irritation, and that cell secretion, nutrition, and antitoxin formation are closely related processes.

RABIES.

BY

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Pathology.

THE morbid histology of the nerve ganglia in rabies has received recent investigation (1889–1900) which has evoked discussion and contention. Van Gehuchten and Nelis maintain that these lesions are of paramount importance; Babes, while admitting their existence, deems them less manifest than those of the brain and cord.

On section of a ganglion we find angular or ovoidal nerve cells, each cell situated in a somewhat circular space, which is bordered with connective-tissue corpuscles. The surrounding tissue is slightly fibrillated with its corpuscles not very numerous. In rabies the corpuscles around the nerve spaces become detached; there is also a hyperplasia of connective-tissue corpuscles, especially marked at the boundary of the ganglion. The size of the cells and corpuscles varies according to the animal from which they are derived. In the dog, man, and rabbit the corpuscles are so large that they have been designated epithelioid and embryonic; in the cat and pig they are so small as to resemble leucocytes under moderate magnification. This cell hyperproliferation is sometimes so excessive as to form in spots microscopic nodules, suggestive of analogy to lepra or other infective granulomata (Nelis). This over-production of corpuscles may be all that is observed if the animal has been killed after having been sick for a not very long time; if very early killed there may be little or no change; when permitted to die, the appearances are more graphic; the cells also become involved, some being pallid, faintly granular, and much enlarged. Their protoplasm is vacuolated and the cell contour may present crescentic or hemispherical scallops. The nucleus may be displaced or extruded, it becomes indistinct, and in an occasional cell it undergoes degenerative proliferation, forming a coarsely granular mass or somewhat rosette-shaped figures, or it may become pale, enlarged, distinctly circular, sharply outlined, and pigmented; in this

latter form it is sometimes found outside the nerve cell in the tissue. Finally, the nerve cells, in greater or less numbers, become destroyed and disappear, leaving vacant spaces. Alongside the blood-vessels there is often very decided leucocytic extravasation.

Van Gehuchten accredits Nepveu with priority in discovery of these lesions; remarking that he (Nepveu) "did not attach the least importance to these investigations"; subsequent investigators have attached too much importance to them. In 1872 Polaillon and Nepveu noted characteristic lesions in a man dead of rabies. The whole cerebrospinal axis was the seat of a strong congestion. The ganglion of Gasser was not excepted from that hyperæmic state; it was infiltrated with round or oval cells. "These cells were found in large numbers around the ganglion cells, twelve or sixteen and sometimes more. Some among these cells have a hyaline aspect and are probably epithelioid cells of the capsule of the ganglion cells." The presence of these cells had modified the aspect of the nerve cells, which were jagged, irregular, shrunken, and also deprived of coloring matter. In some rare spots the white cells were aggregated in a focus (J. Crocq). These investigations remained for twenty-eight years a dead letter (Babes). Then Van Gehuchten and Nelis revived, elaborated, and laid stress upon them (1889, 1890). "It is in the peripheral nerve ganglia, the cerebrospinal, and sympathetic, that the rabic virus exercises, by preference, its deleterious action. Rabies seems to us to be a specific affection of the peripheral neuron of sensation. The rabid animal is paralyzed because it is insensitive." The lack of muscular sense may explain its incoordination. Babes asserts: "I have had occasion to study two cases of rabies in man, in both the sensibility, carefully examined in the paralyzed parts, was intact." Babes in 1892 remarks, not, however, referring to the ganglia: "That which above all characterizes the lesion is the presence of the pericellular nodules—the collection of cells about the nerve cells, which has been termed the rabic tubercle."

Van Gehuchten and Nelis claim that the rabic tubercles of Babes have not the importance attributed to them by that investigator. "They did not exist in our two cases of human rabies. Babes himself affirms that they are in default in animals inoculated with the fixed virus. The lesions described up to the present are not then of a character sufficiently specific to enable them to be useful as an element of diagnosis." The foregoing observations are made by Van Gehuchten and Nelis regarding the researches of others, especially of Babes.

Van Gehuchten further states: "It is necessary to examine the ganglia of the dog dead of natural rabies. M. Crocq forgets that if, in rabies determined experimentally by the fixed virus, the ganglionic lesions are wanting, so also are the vascular and cellular lesions, as

Babes has shown a long time since." Therefore, so far as the fixed virus is concerned, the revelations of Van Gehuchten, Nelis, and Babes are all equally at fault. Evidently the fixed virus should exhibit the essential lesions of rabies. All other lesions must be non-essential, attributable to concomitant, not causal organisms. Most typical rabies may then exist according to Babes, Van Gehuchten, and Nelis, with the lesions described by them eliminated, thus proving that they are non-essential. Admitting the fact, it is impossible to escape the logically demonstrated conclusion which deprives the lesions in question of the slightest claim to specificity. "The street virus and the fixed virus must present profound differences between themselves, and as the fixed virus comes from the street virus, one must admit that its mode of action upon the organism arises insensibly during its passage from one animal to another" (Van Gehuchten and Nelis). This is an explanation which does not explain. In point of fact, rabbits dead of the fixed virus subdurally inoculated do exhibit in their ganglia the lesions in question. They may not all do so, many may not do so; but if any do, it is sufficient to prove the affirmative assertion. There are in my possession ganglia of rabbits of the 573d passage (Paris virus), and of the 267th passage (virus introdued by the writer, starting from the medulla oblongata of a rabid cow); these ganglia present exquisitely the morbid morphology of rabies, which has been erroneously supposed to be restricted to animals dead of the street virus. Golgi, using a fixed virus, makes the following observations, which exactly apply to the condition of the ganglia above referred to: "I have always found the intervertebral ganglia changed; although these changes were inconstantly localized in the different groups, the entire picture was absolutely characteristic. Besides the well-known round-cell accumulation and vascular dilatation which have often been spoken of, I want to emphasize especially the vacuole formation, which takes place to such extent as to give the cell a cyst-like appearance; further, the coarsely granular condition of the cell protoplasm, which chiefly takes place in the centre, being surrounded by a peripheral homogeneous zone; then the displacement of the nucleus toward the periphery, the nucleus at the same time appearing elongated, gives the impression as if it had been compressed. The nucleus is often found at the extreme edge of the cell, where it might be very easily overlooked; in a few cases it is found outside the cell under the cell membrane. The peripheral homogeneous zone is most often found in the cells, which show a coarsely granular interior, and in these cells the nucleus is occasionally formed by an accumulation of chromatic particles in a condition of advanced regressive metamorphosis."

In an article entitled "Les Lésions Anatomo-Pathologiques de la Rage sont elles specifiques," J. Crocq concludes:

"1. Neither the vascular nor the cellular lesions described by authors anterior to Van Gehuchten, nor the capsular lesions of that author are, properly speaking, specific of rabies. The first are only manifestations of an inflammation and of a profound infection of the nervous centres; the second appear to be the result of special conditions, in which organisms profoundly intoxicant are found.

"2. The anatomo-pathological lesions of rabies actually known may be encountered in other maladies.

"3. Rabies consists in a toxic infection very acute, provoking profound alterations, chemical and physical, without proper specificity, in the nerve axis, and in the peripheric ganglia.

"4. The pathological physiology of rabies explains itself relatively easily by lesions vascular, cellular, pericellular, and chemical, extending themselves to the whole nervous system, central and peripheral.

"5. The aspect of the ganglion knot of the vagus in animals dead of street rabies (rage des rues) is so special, so characteristic, that the microscopical examination of this ganglion actually remains the method most simple and most sure to establish the diagnosis of rabies in the dog which bites.

"6. If the ascertaining of that lesion permits us to affirm probably rabies in the dog which bites, its absence does not suffice to exclude in a manner absolutely decisive the rabic infection."

M. Cornil asseverates: "The examination of nerve ganglia at this point of view is most difficult. For a long time the normal conjunctive (lymph?) path has been taken for a lesion. As to the cellular lesions it is only recently that they have been studied, thanks to the progress of technique."

Prof. Henry J. Berkley, of Johns Hopkins University, and Prof. Camille Golgi, of the University of Pavia, are the chief exponents of the advanced technique as regards rabies. Berkley's work is restricted to the cerebral and cerebellar cortex; Golgi's researches include also the ganglia. These authorites are not in accord, though their differences are not irreconcilable. Both used a fixed virus. Berkley finds a paucity of lesions and generalized; Golgi, an abundance and localized.

Berkley failed to find any evidence of coarse lesions of the vessels in the form of extensive hyperæmias, plastic exudates, and extensive emigration of corpuscular elements into the perivascular sheaths, nor could a single extravasation of the red blood corpuscles be found as has been described by Popoff and others in the human subject (this must have been infection with street virus). "The sheaths of the vessels are not greatly altered, the endothelial nuclei are not swollen, some of the nuclei of the muscularis show a tendency to absorb less of the aniline stain than usual and show vacuoles, but the muscular fibres

are not swollen or hyaline and altogether the evidence of a degenerative process taking place in the walls of the nutrient vessels is inconsiderable.

"We have, therefore, in the present cases only the indications of a mild infection, of a sufficient intensity, it is true, to cause death after the lapse of a considerable number of days, but insufficient to cause any considerable morbid change of the vascular walls, together with a degree of leucocytosis such as is often found when the soluble poison of bacterial source acts with a considerable degree of energy upon the blood-forming organs.

"These conditions are therefore most favorable to enable one to ascertain the effect of the subtle poison from the rabies bacterium upon the nerve elements. Golgi's cases, in which he found karyomitoses of the nuclei of the vascular muscles, must have been of greater severity, and the damage to the nutrient supply have borne its part in the production of the nerve-cell changes which we are now able to exclude to a certain degree.

"*Alteration in the Nerve Elements Found in the Nissl Preparations.*—Interest in the stichochromic cells of the cortex centres not in the protoplasm, where indeed alterations are ill-defined, but in the contents of the central vesicle. In the place of the clear vesicle holding a nucleus and a variable number of adnucleolar particles in a clear karyoplasm, we have now its contents everywhere turbid and more deeply stained than normal, the nucleolar particles showing a variety of dispositions. They are roughened and much larger than ordinary, so much so that the actual nucleolus is no longer distinguishable from them. These particles are either scattered equally through the karyoplasm, or are segregated toward the central nuclear point and form figures similar to those found in chronic alcoholism, though less pronounced, as the extreme degree of roughness is no longer seen. Very few nuclei can be discerned showing the normal disposition of the chromatin particles. In a few of the largest pyramidal cells where the lesions of the nuclei are not far advanced and the nucleolus can be determined, it has the appearance of being empty of all contents, the central portion remaining unstained, with a surrounding deeply dyed membrane, from which numerous projections pass an infinitesimal distance toward its centre. Vacuolation of nuclei was also seen by Popoff, who figures a certain roughness of the nucleolar particles, less pronounced than in the present instances.

"*Changes in the Nerve Elements Seen with the Silver Phosphomolybdate Method.*—The lesions of the cortical cells in hydrophobia, as seen with this method, are on the same order as those induced by other irritants to the tissues of the region, but present some slight differences from those we have already studied. The distribution of the pathological

changes is very widespread among the cortical cells, which are no longer present in groups and certain regions of the cellular layers, as is the rule with some of the weaker toxins. Everywhere in a section the dendrites of the cells are found to be involved in the degeneration, and it is rare to see a cell in which all the various branches have been completely spared. The tumefactions are frequent along the stems, but are all of small size; and the portions of the dendrite intervening between the swellings are thin and have but very few of the gemmules still adherent to them, and of these remaining still fewer show perfect staining. On the swellings the lateral buds have completely disappeared, and left no trace of their former presence. A very careful search had to be made to discover any completely normal cells among the diseased ones.

"But few of the corpora show distinct implication in the process of degeneration. An occasional one may be found having some erosion of its body, but these are rare. Lesions of the neuraxon in the form of beaded swellings, such as Golgi has described, appear to be infrequent, for in the series of several hundred preparations not more than half a dozen such cylinders could be found.

"Neuroglia alterations are likewise not definite. There is certainly no multiplication of either the star-rayed neuroglia or the vascular cells; the latter may now and then show bodies and virus that may possibly be a little tumefied, but it is hardly sufficient to enable one to state that it is a distinct alteration. Golgi figures granular, fatty degeneration of the neuroglia cells diffusely scattered through the entire nervous system.

"The branches of the Purkinje cells show a small percentage of swellings. Some of the knots are of considerable size and are well stained. The lateral buds are retained in part upon these swellings, while otherwise the branches show no diminution of the protoplasmic fur, in strong contrast to the projection cells of the cerebrum, evidencing that they are capable of greater resistance to the effects of this, as well as other poisons, than the cerebral elements. The other nerve elements of the cerebellum are not sufficiently frequently stained to permit one to determine with certainty whether they are abnormal or not. The neuroglia elements have the same conditions apparent in them as in the corresponding elements of the hemispheres.

"This investigation departs in a number of particulars in its results from the one by Golgi. We find the degenerated cells universally present in every portion of the cortex, while he sees them only freely distributed. More important is the supposed primary involvement of the nerve cell and afterward the dendrites to their terminations. This is entirely contrary to the results obtained in any of those studies on the action of poisons on the nerve cells (alcohol, serum, ricin), and

is against the law of degeneration of the nerve cells for the element to die from its centre outwardly; either the lesion begins at the periphery and extends centralward, or all the component members of the cells undergo necrosis synchronously. Golgi makes no mention of the condition of the gemmules on the dendrons in these atrophic conditions. It is extremely probable that his stain failed to color them at all, otherwise it is hardly possible that he should have overlooked such an important and readily distinguishable feature of cell degeneration as their shedding represents.

"While it is true that the same swelling of the axis-cylinder fibre was found in this study as had been previously described, the lesion must be held to be a rare one, and not of sufficient frequency to constitute one of importance.

"I can see no signs of anything approaching an inflammatory process taking place in the cerebral tisues, only the indications of a purely degenerative reaction from the effect of the toxic substance produced by the bacterium of hydrophobia, essentially causing the same pathological changes as those induced by other soluble poisons when present in the circulation in sufficient quantity to disturb tissue nutrition."

The investigations of Berkley are quoted thus in detail because they set forth the essential lesion of rabies in the structures examined.

Inflammation consists of a group of features; it is impossible to designate the essential one. A feature may be pointed out as absolutely indicative of inflammation, *e.g.*, pus or fibrin formation, but inflammation may exist without these features. It may be too restrictive to assert that leucocytic extravasation is the essence of inflammation; a degenerating vessel wall may permit this. It is certain that in rabies leucocytic and erythrocytic extravasation does occur. If the definition of inflammation be, some effect on the vessel wall allowing corpuscular extravasation, then Babes and others, referring to microscopic lesions in the nervous system as inflammatory, are entirely correct. It is certain that the coarse lesions of inflammation are not found in rabies as in infectious diseases and septicæmias. There are no coarse lesions of meningitis, myelitis, peri- or endocarditis, pleuritis, pneumonitis, peritonitis, so common as effects of phlogistic bacteria.

It may be regarded as axiomatic that histogenesis exhibits the same morbid morphology in absolutely diverse diseases; there may be a varietal distinction, for the most part finely microscopic and difficult of detection.

Etiology.

In relation to the as yet (1902) undiscovered cause of rabies, the researches of Bruschettini are interesting. The following is extracted from "La Rage" by Dr. Auguste Marie: "Starting with the idea that the microbe of rabies required for its development the nerve chemical products, the author prepared a jelly adding lecithin from the yolk of eggs or cerebrin extracted from the brain of the dog or rabbit. Upon agar tubes were sown particles of the bulb (medulla oblongata) of a rabbit killed by the fixed virus. After twenty-four or thirty-six hours' sojourn in the oven, confluent colonies appeared, very small, transparent, and difficult to see with the naked eye, resembling little drops of water. These were dispersed lightly on the surface of the jelly; it is easy to resow and to obtain successive generations. By a strong enlargement these colonies appear irregularly dentated along the border, with a dark zone in the centre. These colonies consist of bacilli, short, very small, thick-set. They color easily with Ziehl and the blue of Loeffler. The staining causes to appear at the centre of the microbe a clear zone as in the diplococcus of Fraenkel. In liquids, such as bouillon of brain with the addition of glucose and glycerin, coccal forms are seen to develop which in old cultures are colored violet-red by the Loeffler blue. The microbe grows well at 16° C. (60.8° F.). Its development is slowed in vacuo; it is non-motile.

"The subdural injection of these cultures killed rabbits in from five to eight days, with all the signs of rabic paralysis, and the inoculated medulla transmitted rabies in series. Finally, the microbe was found in sections of the nerve centres in the rabid animals and in those which had succumbed to the injection of the bacillus of Bruschettini.

"The experiments of Bruschettini were repeated at the Institut Pasteur. There it was found that the nerve centres of rabid rabbits presented a microbe responding to the description which we have given. This bacillus was easily cultivated in the media indicated, and its culture provoked in rabbits the phenomena of paraplegia. And yet this microbe is not that of rabies because it is found (with a little less frequency, it is true) in the nerve centres of rabbits not rabid; moreover, inoculation of the dog with the microbe has not been known to provoke furious rabies. Finally, we cannot succeed in rendering refractory to rabies the animals inoculated with the culture of that bacillus."

It may be conjectured that such an organism as this, or one analogous to it, may have caused the general paralysis, recorded as having occurred in three persons under treatment.

Diagnosis.

The outcome of the pathology should be the diagnosis, but there is a conflict of opinion regarding the interpretation of this morbid histology. Microscopic appearances closely resembling, if not identical with, those found in rabies are present in many totally different diseases, especially in uræmic and septicæmic conditions. Babes asserts that the lesions of tetanus above all closely resemble those of rabies; so also do those of puerperal eclampsia (nephritic), but the small cells are not evidently connected with the vessels, nor are they more disposed around the nerve cells. The morbid histology is essentially the same whether in brain, spinal cord, or ganglion, except that in the latter the normal cells, being arranged in capsules lined with endothelial cells, give a different varietal morphology to this lesion.

Babes, while admitting that the lesions of rabies have nothing absolutely characteristic, and that in a marked case of diffused myelitis one might find similar lesions, says: "It must nevertheless be admitted that neither in books nor in my personal experience have I ever met a case similar; therefore up to the present (1900) we may regard rabies as characteristic." To assure himself of the specificity of the lesions found in rabies, Babes examined a considerable number of specimens from dogs and men dead of acute affections of the nerve centres. He observed sometimes vascular lesions much more intense and foci much more extensive than in rabies, but he did not find the embryonic foci around the nerve cells. On this last point Babes fixes the diagnosis. Future observations will probably show that it is not restricted to rabies, in which it is not always present. Referring to ganglionic lesions he (Babes) depreciates their diagnostic value in the following remarks (with which the writer inclines to agree):

"In my memoirs on the pathology of the spinal ganglia I have described similar lesions in many diseases, and I have insisted upon the difficulty of appreciation of lesions less grave because of the varied aspect of the normal ganglion cells, which often are found to be discolored (decolorized), and also without nuclei in normal ganglia. Moreover, the chromatic elements of the cells are of different types and more difficult to appreciate than in the large cells of the cord. Finally the nuclei of the ganglion cells are sometimes displaced in the normal state; also the number of cells bordering the elements (nerve cells) multiply themselves with facility as a result of different irritations."

These ganglionic lesions are often present in rabies and not seldom in other diseases, which, however, with the exception of septicæmia and tetanus are not common in the lower animals; especially is the latter uncommon in dogs. In human beings I have observed the gan-

glionic changes in trauma of the spinal cord due to fracture of the vertebra, in tetanus, in malignant scarlet fever, and in diphtheria, in both of which death was caused by septicæmic infection; also in electrical death when not instantaneous, and in a case of pleuropneumonia in a dog.

The large proportion of suspected animals that do have rabies is remarkable. In one hundred and fifty-seven cases, nearly all dogs, tested by subdural inoculation of rabbits, there were only four which did not develop rabies. In thirty-one cases in which ganglia were examined and positive lesions found, there were three cases, dogs, from which the rabbits subdurally inoculated did not develop the disease; one cat and one pig gave positive results.

The large majority of authorities assent to the following propositions of M. Hebrant: "The value of this positive lesion seems to us at the present time (1900) sufficiently established. Therefore in our opinion it is possible to advance the following conclusion: Whenever in a suspected dog (or, of course, other animal) the microscopic examination of the ganglia allows us to see the lesions pointed out by MM. Nelis and Van Gehuchten, it must be declared that the animal is positively mad. The ganglionic lesions noted by Van Gehuchten and Nelis in street rabies are not constant. The absence of the lesions does not permit us to exclude in a decisive manner rabic infection."

The pathological diagnosis, in itself so interesting and instructive, has no bearing upon the practical question of treatment. If the result is negative, it does not exclude rabies; if positive, the patient is to be treated. Under these circumstances the patient must be treated anyhow, irrespective of the pathology. Furthermore, it is inadvisable to communicate the pathological results to those concerned, because the final, demonstrative confirmation depends upon animal experimentation. If from a suspected animal other animals be experimentally infected with rabies, and rabies be passed from these to another series, it permits us to affirm, beyond the possibility of doubt, the presence of rabies in the suspected animal. Though an affirmative diagnosis of rabies can thus certainly be made experimentally, a negative diagnosis cannot be made in the same way. The absence of rabies in the suspected animal is that which those bitten most ardently desire to know. In either case the experimental result approximates certainty much closer than the findings or non-findings of pathological investigation.

The operator who makes the experiment should be skilful. He trephines and inoculates subdurally four rabbits, one on each of four successive days, or two on each of two successive days; between the operations the medulla oblongata, portions of which are inoculated, should be kept in sterile test tubes on ice, and if at all decomposed, it

should be immersed in neutral glycerin. Should these rabbits fail to develop rabies at the usual time, twelve or fifteen days after the operation, and if, at the expiration of three months, they are still well, unless the virus in the medulla oblongata has been destroyed, the animal in question did not have the virus in its medulla oblongata; in fact, it did not have rabies. The rabic virus resists freezing and putrefaction. It is sterilized at once by a temperature of 118° F. and slowly by one of 108° F. A hot glass rod used in rubbing up the medulla oblongata in water may attenuate or even sterilize the virus; but an experienced operator would not so blunder. Animal experimentation does affirmatively prove the existence of rabies with absolute certainty; it negatives the existence of rabies as certainly as negative evidence can. The microscope does not enable us to arrive at a negative diagnosis; affirmatively it only raises a probability of the presence of rabies. It affords no sure basis for rapid diagnosis of rabies; it is a conjectural diagnosis, contingent upon the absence of numerous disorders.

The following are actual examples of the practical application of ganglionic diagnosis: A bitten person (the ganglionic pathology being present) was assured that the dog was rabid, but later on, the rabbit subdurally inoculated failing to develop, it became necessary to reassure the patient that the dog was not rabid. This was an awkward situation for the doctor, but involved no more serious consequence than loss of confidence. Advice along this line has, however, involved loss of life. Two patients were informed that the ganglia of the dog did not show rabies; it was explained to them that this did not prove the disease absent. They decided to await the result of the experiment, which showed that it was rabies; it was then too late to save these lives. Nothing should have been said to these persons. They should have been simply told that treatment was urgently necessary. "No doubtful balance of rights and wrongs" should be submitted to the average human mind which cannot digest the *pro* and *con* of abstruse data.

Diphtheria clinically and experimentally may give rise to symptoms closely resembling rabies. Such cases, especially if the persons have been bitten by a supposed rabid animal, may be mistaken for rabies. It is well known that the bacillus diphtheriæ may be found in various organs and in the nervous system, medulla oblongata, ventricles, etc. A very interesting case of this kind is reported by Drs. Head and Wilson, of the University of Minnesota. In about sixty-five days after having been bitten on the left cheek by a dog, a lady developed the signs of rabies; especially the spasm and difficulty in swallowing water. She died in about eleven days. Rabbits subdurally inoculated from her medulla developed, and died with symptoms of, rabies. In

the nervous system of the dead woman and in the rabbits the bacillus diphtheriæ was found. Rabbits hypodermatically injected with diphtheria antitoxin and afterward injected subdurally with the supposed rabic medulla oblongata escaped infection. The diphtheria antitoxin does not protect against rabic inoculation.

The writer injected subdurally a hen with the egg of another that had died of rabies. After a prolonged incubation the subject of this experiment developed a paralysis like that of rabies. Opening by chance its beak, the mouth and throat were seen to be full of diphtheritic membrane. Of course the paralysis was diphtheritic.

Treatment.

In order to determine the value of treatment it is necessary to know the natural history of the disease; how the disease behaves when not treated at all. Of persons bitten by rabid dogs, how many develop rabies when not treated? From 1850 to 1872, which period antedates the Pasteur treatment, an annual average of 30 persons died of rabies in France; during the above period (twenty-two years) 660 persons died of this disease. Contrast with this the statistics of the Institut Pasteur, Paris, which show that from 1886 to 1896 inclusive, of 2,730 persons bitten by animals experimentally proven rabid only 19 died of the disease; also the following tabulation from the same years:

	Cases.	Died.	Mortality. Per cent.
A	2,730	19	0.69
B	11,629	56	.48
C	4,286	15	.35
	18,645	90	0.48

Table A includes cases in which the biting animal was experimentally demonstrated rabid.

Table B includes cases in which the biting animal was certified rabid by examination of a veterinarian.

Table C animals suspected to be rabid.

	Cases.	Died.	Mortality. Per cent.
Bitten on the head	1,608	21	1.36
Bitten on the hands	10,254	49	.47
Bitten on the limbs	6,783	20	.29
	18,645	90	0.48

The schools of Alfort, of Toulouse, of Lyons, of Berlin, give one-quarter or even one-third as the proportion that take rabies after having received infected bites, which accords with the experimental results of Hertwig, who produced rabies six times in sixteen subcutaneous inoculations, and of Renaut, who in one hundred and sixty-six injections beneath the skin obtained sixty-seven positive results. The seat of the injections and the animals used should be stated. Deep injections in the cervical region cause rabies much more frequently than those into the back or belly. Using the latter sites, the writer subcutaneously injecting guinea-pigs had only one successful case in sixteen. Difference in locality might explain the disagreement with Hertwig's result, who may have deeply injected the neck. In the experiment the insertion of a definite quantity of virus is insured, which is not always so in bites as they naturally occur, especially in those through clothing. At first view experimental inoculations seem to be more sure to give positive results and therefore more dangerous; but further consideration shows that the situation, the multiplicity, and the character of the natural inoculations (bites) must be given due importance in estimating their gravity.

How many bitten by dogs demonstrated rabid escape when not treated? Previous to the Pasteur epoch (1885) there was no accurate method of demonstration; subsequent to this period very few of those bitten by suspected dogs remain untreated. The diagnosis of rabies, independent of experimental demonstration, is seldom wrong. What percentage of those bitten by dogs suspected to be rabid develop the disease? The estimate of five per cent., ascribed to John Hunter, is the "*pièce de résistance* of those who discredit the Pasteur treatment." This percentage may in the ordinary run of bites be accepted as correct; but assorted statistics, based on the site, number, and character of these wounds very much raise the estimate. Severe and multiple bites on the head, face, and neck when untreated will give more than 50 per cent. mortality. The John Hunter figures show that 5 out of 100 bitten by rabid dogs die if not treated. It is not pleasant to be in a category of 100 of which 5 are due to die of rabies in ninety days more or less. The Pasteur Institute figures show that better things are in store for those treated. Of 2,730 bitten by dogs demonstrated mad 19 died (0.69 + per cent.), less than half the annual death rate of Baltimore City, which is 1.74 per cent. "If with Högyes one recapitulates the average of mortality established in 24 antirabic laboratories, it is found that of 54,620 persons treated 423 died, which gives about 0.77 per cent. It is well to remark that in several of these institutions many wolf bites are treated, which are very dangerous because of their seat, multiplicity, and depth. It must be admitted, on the other hand, that many of the individuals treated may not have

been bitten by rabid animals." The first of the following tables is arranged in the categories A, B, C; the second according to the gravity of the infected bites, as indicated by their situation. The tables are from "La Rage" (Marie), who quotes them from Högyes.

Some of the subjoined tables set forth the results of treatment, which offer as reliable reasons for action as are attainable in the ordinary transactions of daily life.

FIRST TABLE.—CLASSES A, B, C.

Antirabic Institutions.	Years.	CLASSES A AND B.			CLASS C.		
		Persons treated.	Deaths.	Mortality. Per cent.	Persons treated.	Deaths.	Mortality. Per cent.
Paris.....	1886–1895	13.429	71	0.52	3,840	12	0.36
Naples	1886–1895	980	10	1.03	289	2	.69
Turin.....	1886–1894	1,926	21	1.09	281	0	.00
Totals.....	.....	16,335	102	0.62	4,410	14	0.31

SECOND TABLE.—ACCORDING TO THE SERIOUSNESS OF BITES.

Antirabic Institutions.	Years.	HEAD AND FACE.			HANDS.			FEET, TRUNK, COVERED REGIONS.			TOTALS.		
		Persons treated.	Deaths.	Mortality. Per cent.	Persons treated.	Deaths.	Mortality. Per cent.	Persons treated.	Deaths.	Mortality. Per cent.	Persons treated.	Deaths.	Mortality. Per cent.
Paris....	1886–1895	1,508	19	1.26	9,551	48	0.50	6,283	16	0.25	17,337	83	0.47
Turin ..	1886–1894	169	6	3.54	1,260	14	1.11	778	1	.12	2,207	21	.95
Naples..	1886–1895	84	4	4.76	672	7	1.04	513	1	.19	1,269	12	.94
Pesth ..	1890–1895	479	24	5.01	1,983	22	1.10	2,452	13	.53	4,914	59	1.20
Totals		2,235	53	2.37	13,466	91	0.66	10,026	31	0.30	25,727	175	0.68
First treatment by dried cords		320	21	6.56	1,408	17	1.20	1,682	13	.77	3,410	51	1.49
Second treatment by dilutions.....		159	3	1.88	575	5	.86	770	13	....	1,504	8	.53

The method of graduated virulent dilutions used by Högyes deserves notice. In cords dried over caustic potash (Pasteur method), the virulence does not always conform to their age; that is, cords which have been drying for a long time may be more virulent than those which have been drying for a shorter period, whereas the reverse should be the result. This variability is caused by the varying size of the cords; cords unequally thick dry themselves unequally, so that the virulence does not decrease uniformly and by regular degrees, according to the age of the cord. Högyes hoped to guard against these inconveniences by replacing the dried cords with a diluted fixed virus. He bases his views upon those of Pasteur, who asserts that desiccation

in diminishing the virulence does not change the quality of the virus, but its quantity alone. Högyes takes 1 gm. of the bulb (medulla oblongata) of a rabbit that has died of the fixed virus. This is rubbed up as finely as possible, with the precautions of ordinary cleanliness, and very gradually to it is added liquid (*solution physiologique*) 0.6-per-cent. salt solution in the proportion of one part of nerve substance to one hundred parts of the solution. The 1:6,000 dilution does not kill rabbits. The 1:5,000 dilution does not surely give rabies and the incubation is very long. The 1:10, 1:100 and 1:200 dilutions are as active as the most concentrated. The dilutions seem necessary in order to secure immunization. The result of treatment before and after infection varies. If the animal be treated before infection, it is protected in the majority of cases against every mode of inoculation of virus, the most intense trephining and subdural inoculation included. The treatment is of no avail when it follows an intracranial inoculation of fixed virus; also after the street virus similarly inoculated. Treatment practised in the trachea, subsequent to inoculation, prevents the disease one time out of five. It is entirely otherwise with bites and subcutaneous injections. Of eight dogs so treated not one contracted rabies, whereas of the eight control dogs bitten by the same animals five became sick of rabies, four died, and one was saved. Experiments in seventy dogs gave like results.

The following comparisons may be made between the virulence of dried cords and that of the dilutions. From the 1:10,000 up to the 1:6,000, the dilutions correspond to the series of cords from the fourteenth to the eighth day. Injected under the dura mater they give rabies only exceptionally. The 1:5,000 dilution does not kill all the rabbits, or the sickness does not show itself until after a long incubation; it is equivalent to a seven-day dried cord. The 1:1,000, the 1:500, the 1:200 dilutions correspond to the sixth-, fifth-, fourth-day dried cords.

The virus is probably not equally distributed throughout the medulla oblongata. The fourth ventricle is supposed to be especially virulent, so that the better procedure might be to rub up the entire bulb and then take 1 gm. of this material. This method of Högyes is exact and the results of treatment are good.

BITES ON THE HEAD AND FACE.

Day of the inoculation.		Degree of the dilution.	Quantity in cubic centimetres.
First	morning	$\frac{1}{10000} + \frac{1}{8000} + \frac{1}{6000}$	3 to 3 to 3
	evening	$\frac{1}{6000} + \frac{1}{8000}$	3 to 3
Second	morning	$\frac{1}{6000} + \frac{1}{8000}$	3 to 3
	evening	$\frac{1}{10000} + \frac{1}{8000}$	1½ to 1
Third	—morning	$\frac{1}{8000}$	1

BITES ON THE HEAD AND FACE.—*Continued.*

Day of the inoculation.		Degree of the dilution.	Quantity in cubic centimetres.
Fourth	morning	$\frac{1}{5000} + \frac{1}{5000}$	3 to 3
	evening	$\frac{1}{3000} + \frac{1}{1000}$	2 to 1½
Fifth	morning	$\frac{1}{1000} + \frac{1}{500}$	1½ to 1
	evening	$\frac{1}{300}$	1
Sixth	morning	$\frac{1}{5000} + \frac{1}{5000}$	3 to 3
	evening	$\frac{1}{3000} + \frac{1}{1000}$	2 to 1½
Seventh	morning	$\frac{1}{1000}$	1½
	evening	$\frac{1}{500}$	1
Eighth	—morning	$\frac{1}{300}$	1
Ninth	morning	$\frac{1}{5000} + \frac{1}{5000}$	3 to 3
	evening	$\frac{1}{3000} + \frac{1}{1000}$	2 to 1½
Tenth	morning	$\frac{1}{1000}$	1½
	evening	$\frac{1}{500}$	1
Eleventh	—morning	$\frac{1}{300}$	1
Twelfth	morning	$\frac{1}{5000} + \frac{1}{5000}$	3 to 3
	evening	$\frac{1}{3000} + \frac{1}{1000}$	2 to 1½
Thirteenth	morning	$\frac{1}{1000} + \frac{1}{500}$	1½
	evening	$\frac{1}{300}$	1
Fourteenth	morning	$\frac{1}{5000} + \frac{1}{5000}$	3 to 3
	evening	$\frac{1}{3000} + \frac{1}{1000}$	2 to 1½
Fifteenth	morning	$\frac{1}{1000}$	1½
	evening	$\frac{1}{500}$	1
Sixteenth	—morning	$\frac{1}{300}$	1
Seventeenth	morning	$\frac{1}{3000} + \frac{1}{5000}$	3 to 3
	evening	$\frac{1}{3000} + \frac{1}{1000}$	2 to 1½
Eighteenth	morning	$\frac{1}{1000}$	1½
	evening	$\frac{1}{500}$	1
Nineteenth	—morning	$\frac{1}{300}$	1
Twentieth	—morning	$\frac{1}{100}$	1

BITES ON THE HANDS AND FEET.

Day of the inoculation.		Degree of the dilution.	Quantity in cubic centimetres.
First	morning	$\frac{1}{10000} + \frac{1}{5000}$	3 to 3
	evening	$\frac{1}{5000} + \frac{1}{5000}$	3 to 3
Second	morning	$\frac{1}{5000}$	3
	evening	$\frac{1}{3000}$	2
Third	morning	$\frac{1}{3000}$	2
	evening	$\frac{1}{1000}$	1½
Fourth	morning	$\frac{1}{1000}$	1½
	evening	$\frac{1}{500}$	1
Fifth	—morning	$\frac{1}{300}$	1
Sixth	morning	$\frac{1}{5000} + \frac{1}{5000}$	3 to 3
	evening	$\frac{1}{3000}$	2
Seventh	morning	$\frac{1}{3000}$	2
	evening	$\frac{1}{1000}$	1½
Eighth	morning	$\frac{1}{1000}$	1½
	evening	$\frac{1}{500}$	1
Ninth	—morning	$\frac{1}{300}$	1
Tenth	morning	$\frac{1}{5000} + \frac{1}{5000}$	3 to 3
	evening	$\frac{1}{3000}$	2
Eleventh	morning	$\frac{1}{3000}$	2
	evening	$\frac{1}{1000}$	1½
Twelfth	morning	$\frac{1}{1000}$	1½
	evening	$\frac{1}{500}$	1
Thirteenth	—morning	$\frac{1}{300}$	1
Fourteenth	—morning	$\frac{1}{100}$	1

As director of the Antirabic Department, College of Physicians and Surgeons, Baltimore City, Md., I have heretofore used the second table of the Pasteur method. Recently the third table has been used in a child, aged five years. The treatment was as easily borne as the less intensive. Since any wound, however slight, may cause rabies, there seems to be no reason for difference in the manner of treatment. I incline to think that the intensive (third table) should be used in all cases.

FIRST FORMULA FOR TREATMENT EQUALS FIFTEEN DAYS.

Day of treatment.	Age of the dried cord.	Quantity of the emulsion.	Day of treatment.	Age of the dried cord.	Quantity of the emulsion.
1	14 days	3 cubic centimetres	6	5 days	2 cubic centimetres
	13 "	3 " "	7	5 "	2 " "
2	12 "	3 " "	8	4 "	2 " "
	11 "	3 " "	9	3 "	1 " "
3	10 "	3 " "	10	5 "	2 " "
	9 "	3 " "	11	5 "	2 " "
4	8 "	3 " "	12	4 "	2 " "
	7 "	3 " "	13	4 "	2 " "
5	6 "	2 " "	14	3 "	2 " "
	6 "	2 " "	15	3 "	2 " "

SECOND FORMULA FOR TREATMENT EQUALS EIGHTEEN DAYS.

Day of treatment.	Age of the cord.	Quantity injected.	Day of treatment.	Age of the cord.	Quantity injected.
1	14 days	3 cubic centimetres	8	4 days	2 cubic centimetres
	13 "	3 " "	9	3 "	1 " "
2	12 "	3 " "	10	5 "	2 " "
	11 "	3 " "	11	5 "	2 " "
3	10 "	3 " "	12	4 "	2 " "
	9 "	3 " "	13	4 "	2 " "
4	8 "	3 " "	14	3 "	2 " "
	7 "	3 " "	15	3 "	2 " "
5	6 "	2 " "	16	5 "	2 " "
	6 "	2 " "	17	4 "	2 " "
6	5 "	2 " "	18	3 "	2 " "
7	5 "	2 " "			

THIRD FORMULA FOR TREATMENT EQUALS TWENTY-ONE DAYS.

Day of treatment.		Age of the dried cord.	Quantity of the emulsion.
First	morning	14 days	3 cubic centimetres
		13 "	3 " "
	evening	12 "	3 " "
		11 "	3 " "
Second	morning	10 "	3 " "
		9 "	3 " "
	evening	8 "	3 " "
		7 "	3 " "
Third	morning	6 "	2 " "
	evening	6 "	2 " "

THIRD FORMULA FOR TREATMENT EQUALS TWENTY-ONE DAYS.—*Continued.*

Day of treatment.	Age of the dried cord.	Quantity of the emulsion.
Fourth	5 "	2 " "
Fifth	5 "	2 " "
Sixth	4 "	2 " "
Seventh	3 "	1 " "
Eighth	4 "	2 " "
Ninth	3 "	1 " "
Tenth	5 "	2 " "
Eleventh	5 "	2 " "
Twelfth	4 "	2 " "
Thirteenth	4 "	2 " "
Fourteenth	3 "	2 " "
Fifteenth	3 "	2 " "
Sixteenth	5 "	2 " "
Seventeenth	4 "	2 " "
Eighteenth	3 "	2 " "
Nineteenth	5 "	2 " "
Twentieth	4 "	2 " "
Twenty-first	3 "	2 " "

An important addendum and adjuvant to the Pasteur treatment is that of Dr. Roux, sous-directeur de l'Institut Pasteur. The entire brain and medulla oblongata of the rabbit dead of a fixed virus is immersed in ether and remains in it for forty-eight hours. It is then taken out and allowed to remain uncovered for one hour; afterward it is finely triturated in a mortar, adding gradually 40 c.c. of sterile water. This emulsion is permitted to stand and settle for one hour, though a much less time is sufficient. Of the supernatant fluid 10 c.c. are subcutaneously injected into the walls of the abdomen, in amounts of 5 c.c. injected on one and the other side of the abdomen. The hypochondria and flanks are less sensitive. This operation is repeated once on some subsequent occasion. It is desirable that these injections should be given as early as possible. This method has been used by the writer in every case, now 368 in number, the youngest fourteen months, the oldest over eighty years; and in two patients pregnant six months; there were no bad results in any case; indeed, it seems to be better borne and less painful than the ordinary injections.

Treatment is preventive, but it has no curative effect. Rabbits, chickens, mice, dogs, sometimes recover from the earliest symptoms, but do not survive the development of later signs. If a human being contract rabies he inevitably dies. Those bitten should resort to treatment at once; delay may be deadly. A physician consulted me regarding a bite on his thumb. He had already delayed ten days and proposed further to await the result of an inoculation experiment. He was advised to take treatment at once, but failed to do so. He developed rabies about as soon as the inoculated animals. Two patients were advised to submit to treatment immediately. They re-

fused, stating that they would await the result of the inoculation experiment. Rabies developed almost simultaneously in the experiment animals and the patients. A boy, aged eight years, was brought by his father for treatment. He received two hypodermic injections, 5 c.c. each of emulsion of brain and medulla oblongata. The child made little complaint, but the parent, much excited, vehemently declared that the treatment would kill his child. Against the most earnest protestations he took the child home next day, which was February 5th, 1900. The wounds were multiple and severe. One on the right side of the forehead, one over the right eyebrow, one on the posterior surface of the right upper arm, and one on the right scapula. These wounds had been cauterized with nitric acid and washed with solution of corrosive chloride of mercury thirty minutes after they had been received. Three rabbits subdurally inoculated from the medulla oblongata of this dog developed rabies on February 19th and 20th, fourteen and fifteen days after the operation. A cow bitten by the dog also died of rabies. On February 25th, 1900, the child returned for treatment after an interval of twenty days' suspension. Rabies developed in the child on March 14th, forty days after he had been bitten and sixteen days after resumption of treatment. The child died on March 17th, 1900. A girl, aged six years, was brought to this institution May 23d, 1901, with rabies already developed. She died in one and one-half hours after her arrival, and about thirty days after having been bitten. The wound was across the bridge of the nose on the left side, and had entirely healed. However, a number not treated escape. An example of this was a girl, aged ten years, bitten severely on both bare arms. The dog had been experimentally demonstrated rabid.

Cauterization reduces the liability to rabies almost one-half. It should be early resorted to, but in many cases it is not possible for it to follow the intricacies of the wounds. Immersing the wounded part several times daily in very hot water, to which boric acid may be added, is useful. Serum therapy as a mode of treatment has not achieved success. The following is from Sternberg's "Bacteriology," pp. 334, 335: "In 1894 Tizzoni and Centanni gave an account of experiments made principally upon sheep. By repeated inoculations they succeeded in obtaining from these animals a serum having an immunizing value of 1:25,000 or more, and from this a precipitate was obtained estimated to have a value of 1:300,000, and which in doses of 0.23 gm. (of the dried precipitate), dissolved in five times its weight of water, ought to be a sufficient dose to protect a man from the development of hydrophobia. The authors believe that inoculation with this antitoxin would be reliable for man, and would possess decided advantages over Pasteur's method. These advantages are specified as follows: Applicability at any time during the period

of incubation up to the moment of the appearance of the symptoms of rabies; absolute absence of virulence and of any injurious action; very rapid treatment by the injection of one or several small doses of material; complete solubility and consequently prompt absorption of the material injected, and its long preservation in a dry condition." "He doth protest too much." Seven years have elapsed since these statements were made but no further information has been given. An efficient antitoxin remains an unsatisfied desideratum, and "a consummation devoutly to be wished."

D. P. Blaine, professor of animal medicine, London, about 1818, gives a cure for rabies: "Fresh leaves of the tree box, ℥ ij., of rue, ℥ ij., of sage, ℥ ss." His remark, as follows, is more sage than his remedy: "Out of ten dogs bitten, I believe not more than two on an average escape; but of the same number in the human subject bitten, perhaps not so many as two would become hydrophobious."

Intravenous Injection.—This mode of treatment has not been practised sufficiently often in the human being to determine its efficacy and freedom from risk.

Drs. Novi and Poppi communicated (April, 1892) to the Medico-Chirurgical Society of Bologna a case styled the first cure of a grave case of rabies by intravenous injections; which case has been received with incredulity since Drs. L. de Blasi and G. Russo-Travali failed to cure or to alleviate three cases of rabies treated in like manner. 1st, a girl, aged six years; 2d, a boy, aged seven years; 3d, a man, aged fifty-seven years. The boy and girl were undergoing treatment when rabies developed; thereupon the intravenous injections were given, which were of cords that had dried five, four, and three days. The dose was 3 c.c. of each. The man above referred to had been treated at the Institute of Palermo from December 19th, 1894, to January 9th, 1895, for a previous bite. On September 7th, 1895, he was again bitten by a rabid dog. The wound was on his right hand. He died of rabies December 10th, 1895, notwithstanding intravenous injection. His previously acquired immunity did not last one year. This constitutes an inexact reply to the question, How long does treatment confer immunity?

Dr. Rambaud, director of the New York Pasteur Institute, reports four cases undergoing treatment, to which intravenous injections were superadded. The cases were three in boys, aged four, nine, and ten years respectively, and one in a girl, aged nine years. The nine-year-old boy and girl received each nine intravenous injections in doses of 2 c.c. and 3 c.c. The veins injected were cephalic, basilic, median cephalic, and median basilic. These children had not developed rabies. The most virulent emulsion used was that of a fourth-day cord.

Some Peculiarities of Rabic Virus.—Sternberg asserts that "the virus fixi is destroyed by exposure for ten minutes to a temperature of 60° C. (140° F.), and that a temperature of 55° C. (131° F.) fails to destroy in ten minutes. Marie states that it can be destroyed by heating to 48° C. (118° + F.) for five minutes, a sojourn of one hour at 50° C. (122° F.), or of twenty-four hours at 45° C. (113° F.) suffices to cause the rabic bulb to lose all its virulence." It is very slowly destroyed at 108° F., and not rapidly, as was stated through error in Vol. XV., p. 521.

De Blasi and Russo Travali filtered "sur bougie" emulsions of the rabic bulb and injected the filtrate into rabbits which succumbed to paralysis. Galtier submitted to a temperature of more than 100° C. (212° + F.) the nervous emulsions of rabid animals, and inoculated them into the veins and serous spaces of dogs, sheep, and goats. The animals presented the phenomena of grave intoxication, sometimes mortal. Of course this was the effect of the toxin.

The latent period of rabies which precedes the symptomatic reaction of the malady seems to prove that the rabic virus acts on the nerve centres in secreting a poison—a toxin, of which a certain quantity and a prolonged action upon the cells are necessary for the development of the specific symptoms.

Rabbits inoculated subdurally with the rabic toxin either take nothing, or if they develop paralysis their medullas inoculated convey no rabies.

Sheltered from the air, cold — 24° C. (— 11° F.) and 4° C. (40° F.) has no effect whatever on the rabic virus. The brain of a rabid rabbit has shown itself active even at the end of five months (Viala). Jobert preserved the body of a rabbit for more than ten months at —10° C. (14° F.) and — 25° C. (— 13° F.), and the bulb nevertheless remained virulent. Cold of — 35° C. and — 60° C. attenuated the virulence without destroying it.

The rabic virus preserves its strength for a rather long time in the cadaver, even in a state of putrefaction. Galtier has succeeded in the transmission of rabies by inoculation of the nerve centres from cadavers of rabbits buried twenty-three days and from dogs buried forty-four days. A practical difficulty in determining the existence of rabies in dead animals is the rotten state in which they are received, for the putrefactive organisms kill the experimentally inoculated animals. Putrefactive material, in neutral glycerin, changed as often as its odor remains, has the rabic virus preserved and the putrefactive virus eliminated—destroyed. The glycerin must be neutral and not superabundant. If the glycerin becomes acid, as it is liable to do, the rabic virus is destroyed; and perhaps the same result takes place in vaccine virus. Neutral glycerin at 30° C. (86° F.), other conditions

being equal, is without action on the rabic virus. The bulb of rabid rabbits, preserved for four weeks in glycerin at the temperature of the room, gave the disease as rapidly as the fresh virus. An emulsion rendered decidedly acid to reactive paper by one or two drops of acetic acid or decidedly alkaline with a small crystal of carbonate of soda shows itself inoffensive. Phenic acid destroys the rabic virus in one or two hours, according to its concentration of five per cent. or two per cent. Boric acid is active in fifteen minutes; lemon juice in seven minutes. Nitrate of silver, so often employed, is feeble in action. Sulphate of copper, aqua ammoniæ, hydrochloric and sulphuric acids are active. According to Bakai a solution of ten drops of chlorine in 10 gm. of distilled water destroys the virus completely; it is likewise so with bromine water and the essence of eucalyptus. A solution of 1:1,000 mercury bichloride, freshly made, renders virus inert. Solution of permanganate of potassium, five per cent. to two per cent. in alcohol at 50° to 90° after twenty-four hours destroys the virus. The emulsion in alcohol, 25°, inoculated after twenty-four hours and after three days gave rabies after periods of inoculation which were respectively eight and ten days. Inoculated after five days it showed itself inactive. Alcohol at 15° did not alter the virulence after a contact of seven days. Simple water conserves the virulence from twenty to forty days; so also do bouillon and 0.6-per-cent. salt solution.

The gastric juice exerts an attenuative action on the rabic virus after a sojourn of five hours at a temperature of 20° C. Tizzoni and Centanni utilized this property to obtain a vaccine for sheep, rabbits, and dogs, injecting in them an emulsion prepared after this method. Marie says: "On the same order of ideas we desire to say a few words on the action of bile. Bile, either from a rabid or well rabbit, and emulsion of rabic bulb in equal parts is sterile. Franzius thought that this could be availed of as a protective. He regarded it as of the nature of an antitoxin. Valé repeating his experiments, found that there was no antitoxic action, but that the bile acted as a powerful antiseptic."

In the East the raw livers of rabid dogs are given by the mouth to those bitten.

Light acts powerfully on rabic virus. An exposure of forty hours to sunlight destroys the rabic virus even if the thermometer does not exceed 30°. The increase of atmospheric pressure has no influence whatever, nor have the Roentgen rays.

The immunity given to herbivora and in some cases to dogs by intravenous injection of rabic virus constitutes one of the most obscure questions in the history of rabies. The facts reported in 1881 by Galtier are exact. The injection of rabic saliva, or, better, an emulsion of rabic bulb into the jugular vein of sheep or horse, does not cause

rabies and may confer immunity. MM. Roux and Nocard, in their work on this subject, maintain that it is possible so to protect herbivora even after twenty-four hours following intraocular injection with street virus.

Protopopoff at the same time showed that the intravenous injection of the graduated virus in the dog did not kill it, but gave it immunity. Four dogs were inoculated in the femoral vein with cords of the sixth, third, and first days. After some time they were injected anew in their jugulars. In about a month they were tested by trephining and subdural injection with the bulb of fixed virus. They all remained well. M. Roux established that it was possible to render dogs refractory, injecting them only one time in the veins with a large quantity of cords of very feeble virulence, that of the eighth or eleventh day; but the result was not so constant as in herbivora. In order to explain the foregoing surprising facts Helman ascribed them to the structure of the vessels. The capillaries in the herbivora would oppose themselves to the passage of the virus into the nerve centres, while they would permit it in other animals. The history authorizes no such interpretation. The injection in sheep practised not in the jugulars but in the carotids may be followed by the development of rabies. Inoculated, on the contrary, in the crural artery, the rabic emulsion leaves the animal well. If the rabic virus becomes inoffensive in passing extremely diluted through the pulmonary filter, we do not understand why it should not be so for other animals than the herbivora, and why the injection into the auricular vein should give rabies to rabbits.

SMALLPOX.

BY

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DUBLIN.

Etiology.

CALMETTE and Guérin, in a series of experiments on rabbits with vaccine lymph, found that lymph, taken on the fourth day with aseptic precautions, showed on microscopic examination very few bacteria stainable by ordinary methods, but many very minute refractile motile granules. In glycerinized vaccinal pulp these granules are larger and immobile; and the better the quality of the vaccine the more numerous they are. A skilled observer may indeed affirm with certainty that the vaccine will be good or bad, according to the number of these refractile free granules which the authors suspect to be the infectious agents of vaccina.

Funck, in a preliminary report of studies carried out in the Serotherapeutic Institute of the University of Brussels, states: (1) Vaccina is not a bacterial disease. (2) Vaccina is a protozoal infection; the organism can easily be seen in vaccinal pustules and in active lymph. (3) The inoculation of these parasites in a sterile emulsion causes vaccina in all animals. (4) The inoculation of this emulsion confers immunity against further inoculation of vaccine. (5) The pustules of variola contain a protozoon, which is similar morphologically to that of vaccina. (6) As a result of these experiments it is shown that variola and vaccina are two identical affections, that vaccina is a milder form of variola, and hence the antivariolic immunity, which is produced by vaccination, comes under the general laws of specific immunity. The fact that lymphs preserved in glycerin maintain their characteristic activity shows that this activity is due to some organism other than a bacterium, since they remain absolutely sterile in all ordinary culture media.

Funck suggests the name of *Sporidium vaccinale* for the organism. In a hanging drop the protozoon is seen close to the cover-glass, while the leucocytes fall to the lower part of the drop. He has been able to

separate the protozoa by means of a fine spatula made of platinum wire, under low powers of the microscope, and after washing them twenty to thirty times in a drop of bouillon, has inoculated them into calves and produced typical pustules on the sixth day, the animal also acquiring a typical immunity. Similar structures are found in the pustules of smallpox.

Regarding Guarnieri's much controverted *Cytorrhyctes variolæ* of the group of protozoa, the literature may be consulted in Galli-Valeri's "Kritische Uebersicht über den Zusammenhang der Variola mit Vaccine." L. Pfeiffer, of Weimar, more than ten years ago claimed to have demonstrated an amœboid parasite or sporozoon in humanized and calf lymph as well as in the contents of the pustule of smallpox. In 1892 Guarnieri, of Pisa, published the results obtained by him from observations on the inoculated rabbit cornea. By limiting his investigations to the cornea, he was able to note the histological effects of vaccination uncomplicated by the vascular phenomena of inflammation. In the epithelial cells of the cornea he found peculiarly staining bodies, varying from the size of a micrococcus to about half that of an epithelial nucleus. He considered that he had demonstrated amœboid movements and reproduction processes in these bodies, and founded for them a new genus and species of protozoa, to which he gave the name of *Cytorrhyctes vaccinæ*.

Since Guarnieri's pronouncement in 1892, a fierce academic battle has raged as to the exact nature of the "Guarnieri bodies." Gustave Mann, of Oxford, has failed to convince himself that these bodies stand in a causal relation to smallpox. The opposite view is held by V. Wasielowsky, one of Pfeiffer's pupils, who concludes from an exhaustive experimental inquiry that Guarnieri's bodies are really parasites and the cause of vaccina. The specific nature of these bodies was called in question by Ferroni and Massara in particular. These observers alleged that similar bodies may be produced by all sorts of irritants applied to the cornea. The answer to this objection comes from Guarnieri himself, who so recently as December, 1901, claims to have cultivated his parasite, the *Cytorrhyctes variolæ*, by means of the collodion-sac method, in the peritoneum of rabbits.

Whatever may be the *causa causans* of smallpox, there can be no doubt that various species of pus-producing germs are demonstrable in the contents of the fully formed pustules—*Staphylococcus aureus, citreus*, and *albus* (P. Guttmann), *Streptococcus pyogenes* (Garré). H. Immermann says that "as these ordinary pus cocci are to be met in pus wherever it originates, their presence in the suppurating pock probably merely shows that in variola they are the cause of the secondary suppuration. Of course they cannot be considered as at the same time the true or even the chief cause of variola. An important de-

duction from this finding is that suppuration, although very frequent and almost universal in the usual course of variola vera, is really nothing but a complication of the disease or an accident caused by a different but always accessory or mixed infection."

In my original article on smallpox (Vol. XIII., p. 417), I observed that only upon such mucous membranes as are exposed to the external air are fully developed pustules to be seen, and I added that this fact would point to a secondary bacterial infection by the *Streptococcus pyogenes* as the determining cause of pustulation.

Aerial Convection.—A remarkable contribution to the literature of the aerial convection of smallpox has recently been made by Dr. John C. Thresh, medical officer of health of the County of Essex. The excessive prevalence of smallpox in the Orsett Union, Essex, has of many years been notorious in that county. Investigations made during the years 1892–95 led Dr. Thresh to conclude that the sole cause of this excessive prevalence was the proximity of the smallpox ships of the Metropolitan Asylums Board. This was also the popular view.

The smallpox ships were first anchored opposite Purfleet, a hamlet within three-quarters of a mile radius of the north bank of the Thames in the Orsett Union, early in 1884. Since that time the deaths in the Union from smallpox have proportionately greatly increased. From 1871 to 1883 inclusive the ratio of deaths in the Orsett Union compared with the remainder of Essex was 4 to 3. Since 1884 the corresponding ratio has been 5 to 1.

The present epidemic has afforded Dr. Thresh the opportunity of studying more carefully the effect of the floating hospital in disseminating smallpox. The earliest case of the disease recorded in Essex in 1901 occurred in the last week of August. The patient was a man employed during the day at Purfleet, but residing in Gray's Urban District, which forms part of the Orsett Union. Up to January 31st, 1902, the number of cases in this union was 290, the population being 33,721. In the whole of Essex, exclusive of the Orsett Union, there were 162 cases in a population of 782,700. These figures represent 8.6 cases per 1,000 in the Orsett Union, but only 0.21 per 1,000 in the remainder of the county. In other words, in proportion to the population there have been forty times as many cases in the Orsett Union as in the remainder of the county.

Purfleet is in West Murrick parish. The incidence of smallpox in Purfleet has been, up to January 31st, 1902, at the rate of 88 per 1,000 of the population, in the rest of West Murrock 24, and in the remainder of Orsett Union only 2.8 per 1,000. It will thus be seen that nearly four times as many cases (in proportion to the population) have occurred in Purfleet as in the remainder of West Murrock and

thirty times as many as in the rest of the Orsett Union, notwithstanding the epidemic prevalent in Grays.

There is only one other parish in the Orsett Union which is near the hospital ships. This is Aveley, with a population of 1,061. During the period under consideration, 22 cases occurred in this parish, or 11.3 per 1,000 of the population—a further confirmation of the air-borne character of the infection.

Still more cogent proof, however, is obtained when the relation between the prevalent wind and the distribution of the disease is considered. The wind-rose shows that by far the most prevalent winds have been southwest and west-southwest. In the cottages nearest and exposed to the prevailing winds one out of every eight persons was attacked. If such an epidemic prevalence had occurred in London there would have been over half a million cases in the seven months ending with January, 1902. For years past, Dr. Thresh has been informed, there has been no intercourse whatever between the hospital ships moored in the Thames tideway and the Essex shore. Any infection, therefore, from the ships must have been air-borne.

Dr. Thresh admits that it is exceedingly difficult to ascertain to what distance the infection may be carried by the air, but his impression is that in the direction of the wind it may be carried two, or possibly three, miles.

Diagnosis.

In a paper on the differential diagnosis of smallpox read at a special meeting of the Hunterian Society of London, held on November 13th, 1901, Dr. J. MacCombie, medical officer of the Brook Fever Hospital, pointed out that the diagnosis presents difficulties, first, in the pre-eruptive stage, and, secondly, in the eruptive stage.

In the pre-eruptive stage difficulties often occur in connection with prodromal rashes which may simulate scarlet fever and measles. Prodromal rashes resembling scarlet fever are usually best marked on the trunk, the abdominocrural triangle—a triangle the base of which is on a level with the umbilicus and the apex about eight inches below the symphysis pubis—and the flexor surfaces, and they simulate scarlet fever closely in punctate appearance; but the absence of eruption for the most part on the extensor surfaces, the face, the neck, and the temples, and the exemption from faucial inflammation and submaxillary glandular enlargement should warn one of a diagnosis of scarlet fever, especially if backache is a pronounced symptom. In other cases there is a copious crop of petechiæ in the abdominocrural triangle and other flexures. Now, in scarlet fever petechiæ are rarely noted in the abdominocrural triangle; more often they appear in other flexures.

Some hemorrhagic cases of smallpox show a vivid red erythema involving the whole of the skin of the trunk and the limbs, with petechiæ in the abdominocrural triangle and other flexures, and deep purple or black subcutaneous hemorrhages appear similar to those noted in purpura. The faucial symptoms are unlike those of scarlet fever, and the initial symptoms of smallpox are usually well marked, especially the lumbar pain.

Dr. H. Meredith Richards, medical officer of health of Croydon, observes that in the early stages of an attack severe constitutional symptoms are much in favor of smallpox as contrasted with chickenpox, though vomiting, moderate fever, and pyrexial aches and pains are occasionally found in severe cases of the latter. In smallpox the rash is most plentiful on the face and passes from macule to papulomacule. The only lack of uniformity in smallpox will be due to the fact that the eruption appears first on the face and wrists, and may therefore be more markedly vesicular in these regions than on the rest of the body. The rash of varicella, on the other hand, exhibits no preference for the face, is markedly polymorphic, showing a mixture of papules, vesicles, pustules, and scabs on every part of the body.

Early Smallpox Rashes.—H. Roger and E. Weil, writing in *La Presse médicale* on the prodromal and secondary eruption of smallpox, say that the cases admitted under their care numbered 928, rashes being observed in 171, or 18.42 per cent.

The frequency of such rashes was not the same in the two sexes. Thus of 235 males, 62, or 14.48 per cent., had rashes, and of 493 females, 109, or 22.1 per cent. While rashes occurred in all types of the disease, their frequency increased with the severity of the attack. They were most frequent in hemorrhagic cases, being noted in rather more than 47 per cent. of such cases compared with a percentage of less than 13 in cases of varioloid. In unmodified attacks other than hemorrhagic, the percentage differed but little from 20 in all forms, irrespective of the termination of the cases.

The authors state, with regard to individual rashes, that six varieties were recognized—namely, the erythematous, the urticarial, the morbilliform, the scarlatiniform, the purpuric, and the astacoid. The erysipelatous described in standard text-books was not observed by them.

The astacoid (Greek ἀσταχός, a lobster) rash is never encountered except in cases of the hemorrhagic type, and its appearance is a certain indication of a fatal result. The other rashes, even when general, are practically never seen on the face, while the astacoid is almost always present there as well as in all other parts of the body, so that the patient resembles a boiled lobster. It is not a generalized purpuric eruption, but a uniform coloration, a diffused sanguineous extension.

In certain cases, however, parts of the body are free from the rash, and areas of healthy skin may be found on the lower parts of the thighs, on the legs, or on the forearms. In some regions the color may be of a deep red; in others of a purplish hue, lurid, or even petechial. When it is added that the face is slightly turgid, that subconjunctival ecchymoses soon appear, followed by multiple hemorrhagic spots, or even subcutaneous hemorrhages sufficient to produce large bullæ, it will be understood that the patient presents an appearance such as is seen in no other disease.

Treatment of "Contacts."

Dr. Meredith Richards considers that vaccination of contacts should be performed without a moment's delay, as, in order to inhibit the development of smallpox, we must vaccinate with active lymph within three days of infection with the variolous poison. For instance, if a susceptible patient is infected with smallpox on Monday, vaccination on Monday, Tuesday, or Wednesday will prevent the development of smallpox. If vaccination is delayed till Thursday or some subsequent day up to the appearance of the smallpox eruption, vaccina and variola will appear concurrently. In doubtful cases the household should be vaccinated as soon as the least suspicion of smallpox has arisen. Similarly, variola protects against vaccina, and this immunity to vaccination is occasionally of practical service in demonstrating the real nature of an eruption concerning which diverse opinions may have been expressed. Contacts should be kept under medical supervision until the tenth day after successful normal vaccination, or until three weeks have elapsed since the last exposure to smallpox. Richards also insists very properly that school attendance of children from infected houses should not be allowed during the period assigned for medical supervision of contacts. Adult contacts should not be permitted to go to their work until the house in which the disease has broken out has been disinfected. A daily watch for the advent of variolous symptoms should be kept in all cases.

Vaccination.

Vaccine Lymph and Pulp.—"By lymph," writes Immermann, "we mean only the clear and fluid contents which are found in the well-developed vesicles of vaccina; by pulp, on the contrary, we mean this clear fluid together with the specifically infected epidermic base and with the specifically infected epidermic framework of such a vaccinal pock." For obvious reasons only lymph is taken from a human vaccine vesicle. "In order to obtain pulp a vaccine vesicle (of an animal) is scraped away from the underlying papillæ of the corium

by means of a spatula or spoon-like instrument. The vesicle is to be removed unopened and entire, together with its base of epidermis (the rete Malpighii), and the production of any hemorrhage should be carefully avoided. The partly fluid and partly solid mass so obtained is now rubbed up into an emulsion with a small amount of glycerin (vaccine emulsion). This emulsion is then preserved in gram bulbs under the same precautions as are observed in the case of lymph."

It will be seen from this account that animal pulp contains the effective principle of the vaccine disease in a much more concentrated form than animal lymph, and is accordingly more active in producing vaccina. Besides the constituents of vaccine lymph, genuine vaccine pulp contains many red blood corpuscles, cells of the rete Malpighii, prickle cells, horny cells, and detritus. It forms a reddish-gray mass.

Immermann describes vaccine lymph in the following terms: "The ordinary humanized vaccine lymph is a clear, somewhat sticky fluid of a light yellowish color, and when examined microscopically is always found to contain certain elementary constituents. Very fine fibrinous coagula, a moderate number of leucocytes, and a very few isolated red blood corpuscles may be discerned without difficulty. When viewed under higher powers rather numerous corpuscular elements are observed, which are very small and particularly characterized by their sharply outlined edges (Chauveau). These corpuscles, which are also found in human variolous lymph, approximately resemble the spores of the *Cytorrhyctes variolæ* (L. Pfeiffer), and are probably identical with them. The animal vaccine lymph is thicker and more sticky than the humanized, and contains the same elements."

Recent Evidences of the Protective Value of Vaccination.—The Statistics Committee of the London Metropolitan Asylums Board recently issued a report on the occurrence of smallpox in London in 1901. The report says that during the first part of that year there were but few cases of smallpox in London. At the end of August, however, the disease appeared in epidemic form in the large parishes of Marylebone and St. Pancras, whence it spread to every one of the thirty-one parishes comprising the Metropolitan Asylums district. The grand total of cases that occurred in 1901, and which had already terminated at the date of the report in complete recovery or death, was 1,017. Of these, 247 cases ended fatally, giving a percentage of 24.28 per cent. These cases are divided into the "vaccinated," "doubtful," and "unvaccinated" classes, and show a remarkable vindication of the good effects of vaccination. The subdivisions are as follows: Vaccinated cases, 760; deaths, 108; percentage, 14.21. Doubtful cases, 63; deaths, 41; percentage, 65.08. Unvaccinated cases, 194; deaths, 98; percentage, 50.52. The vaccinated cases undergo a further subdivision into "over twenty years of age" and "under twenty years of age" tables.

It is gathered from these that the mortality among children and young people under twenty was only 1.87 per cent., that among the elders being 17.52 per cent.; of those between thirty-five and forty years of age, who had been vaccinated when young, the mortality rate was found to be 28.95 per cent. These latter figures are a strong argument in favor of revaccination. The report states that "there is diminution in the protective power afforded by primary vaccination after the age of twenty years," and remarks in conclusion that the facts set forth in it confirm the report of the special committee appointed after the outbreak of 1870–72, which strongly advocated revaccination. It is also pointed out that cases, the recovery from which is not yet complete, have not been included in the tables. Their inclusion will ultimately reduce the percentage of fatal terminations.

CANCER.

(THEORIES OF THE PARASITIC ORIGIN.)

BY

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AT the commencement of the twentieth century the great problem of the origin of tumors—like a gigantic sphinx—looms large on the medical horizon.

Of this problem the genesis of cancer is but a part; for between the most innocent and the most malignant tumors there is no specific difference. The teratoid tumor, the dermoid cyst, the lipoma, the "mixed" tumor, the sarcoma, and the carcinoma are but varied manifestations of the same morbid process in different degrees.

Two clearly defined but contradictory hypotheses as to the origin of tumors have been evolved—the one based on the *cell theory* and the other on the *germ theory*.

Briefly stated, the question now is, Do cancers and other neoplasms arise through a modification of the formative process, or are they the outcome of an inflammatory process, owing to the intrusion of micro-organism or other irritants *ab extra*?

Those who hold the former hypothesis look to the biological properties of the cells of the affected part for the key of the problem; whereas the other side refer all the essential phenomena of the disease to the activity of parasitic microbes. Few of those who have lately studied the subject take an all-round view of the matter at issue. The great importance of choosing a working hypothesis is now apparent; for of the two alternatives only one can be true.

Although personally I believe that neoplasms arise mainly from the abnormal play of forces generated within the body, I shall not be able here to discuss this aspect of the question; for the object of the present article is rather to pass in review recent work as to the "parasitology" of malignant disease.

The Microbe Theory.

The microbe theory regards malignant tumors as the product of "chronic inflammation" consequent on "irritation," resulting from the presence in the tissues or in the cells of living organisms *ab extra*. "Irritation" and "chronic inflammation" are essential elements of this conception. Thus regarded, malignant neoplasms should be classed with the infective granulomata.

This doctrine really owes all its popularity to the fact that it offers a tangible and concrete—if empirical—explanation of the phenomena of malignancy. Limited to non-malignant tumors it would probably have gained but few adherents. Hence the battle as to its relevancy has centred round the pathogenesis of malignant tumors.

The explanation of the process is believed to be somewhat as follows: The parasitic microbes cause irritation, the latter causes inflammation, and the combined effect of all three—microbes, irritation, and inflammation—is to endow the constituent cellular elements of the affected part—in some mysterious and incomprehensible way—with such excessive proliferative and disseminative qualities as constitute malignancy. It is thought that the special action of the parasites in causing malignancy is mainly due to the fact that they often penetrate into the constituent cells of the tumor and dwell there. It is, however, a remarkable fact—which none of those who have investigated the subject have yet explained—that the nucleus of a cancer cell affected with "parasites" always appears to be in a state of degenerative, rather than of proliferative, activity. It accords with this that these "parasite-containing" cells are very inapt at proliferation, or do not proliferate at all.

As to the life history of this hypothetical parasite nothing is yet known; but on *a priori* grounds, it is presumed to have some analogy with that of the tubercle bacillus, etc., beginning with a primary inoculation lesion and being followed by generalization. Metchnikoff, however, maintains that it should be classed with the miasmatic diseases, and that—like malaria—it is probably propagated by spores formed outside the body, the incubation period varying from a few days to a few years.

In order to test the validity of such statements as the foregoing, investigators have for some time been very busy in endeavoring to discriminate and isolate these supposed parasites; to get pure cultures of them; and by inoculation to reproduce the disease in animals, afterward recovering the "parasites" from the latter. Such is the aim of all recent researches on this question.

It is necessary to insist on the rigid enforcement of these precau-

tions before arriving at any definitive conclusions; for only thus can we avoid being deceived by what Pasteur calls the besetting weakness of medical investigators, viz., "their unfortunate tendency to generalize by anticipation."

Crookshank says: "It is of very little value merely to detect or artificially to cultivate a microbe associated with disease. We must endeavor to establish its exact relationship with the morbid process; and the determination of the true pathogenic value of a microbe is beset with many fallacies."

In the sequel the necessity for regarding this word of caution will be abundantly manifest; for in this branch of pathological work—more perhaps than in any other—experience is apt to be deceptive and judgment difficult.

Bacteria.

Microbes first began to be heard of in connection with the etiology of malignant tumors early in the seventies of the nineteenth century. It was among the schizomycetes that specific cancer microbes were first alleged to have been discovered. Even as early as 1872 Nepveu had noticed the presence of bacteria in tumors of this kind. Rappin in 1886 and Schill in 1887 demonstrated the existence of diplococci in carcinomatous and sarcomatous neoplasms, and claimed that these were the cause of the disease.

They soon had numerous imitators in Francke, Scheuerlen, Freise, Lampiazi-Rubino, Sanarelli, Kübasoff, and others. As, however, none of them succeeded in reproducing the disease by inoculation with pure cultures, the futility of their claims for etiological specificity soon became apparent, and they have since been entirely abandoned, and have now passed out of recollection.

At the time of its publication in 1887, however, Scheuerlen's pronouncement made a great stir. He claimed to have solved the cancer problem by the discovery of a specific bacillus, and to have reproduced the disease in animals by inoculating them with pure cultures of it. His method was that of cultivating the substance of mammary cancers upon solid media comprising sterilized ascitic and hydrocele fluids. On the third day a growth—in the form of a colorless film, becoming yellowish later—usually appeared, which the microscope showed to consist of short bacilli and spores. The latter—which stained readily with ordinary reagents—he often found in the dried juice of cancers; the former he could not demonstrate in stained histological sections, but he found them in fresh cancer juice. Bitches inoculated in the mammary region with pure cultures of these bacilli developed there in the course of a fortnight a tumor the size of a walnut. When the animals were killed—a month after inoculation—these tumors were

found to be epithelial new formations, in which the spores of the bacilli could be easily distinguished.

Senger, Baumgarten, and others investigating Scheuerlen's bacillus shortly afterward showed that it was nothing but a potato bacillus, one of the several kinds of organisms that grow readily on slices of potato. It was therefore a mere epiphyte, having no etiological relation to malignant disease.

Shattock and Ballance (1887), attempting to get cultures from fragments of fresh non-ulcerated mammary cancers removed with aseptic precautions, and carefully transferred to tubes of beef peptone jelly, beef peptone agar agar, and solidified blood serum, concluded, since no growth took place in any of the tubes, that these tumors contained no microbes capable of cultivation. Similar experiments with sarcomatous and lipomatous tumors gave the same negative results. Moreover, they found that fragments of malignant and other tumors, aseptically treated, could easily be kept sterile for considerable periods, just as could bits of the healthy tissues.

Verneuil (1889), having noticed the frequency with which his operation wounds became septically infected after the removal of cancerous tumors in which there were areas of softening, made special bacteriological examination of these foci, and found that they teemed with various kinds of bacilli and micrococci, several species often being present in the same tumor.

In the same year Zahn by cultivation experiments showed that bacteria may abound in the metastases of cancer, even when the latter have no direct communication with the surface of the body.

Hauser (1890) thinks we need not be surprised to find bacteria in ulcerated malignant growths, since under these circumstances the conditions met with are highly favorable to their growth and development. When microbes are found in metastatic growths Hauser believes that they are carried there by tumor elements detached from the primary focus.

Kübasoff (1890) in carcinomata of the stomach found short, thick bacilli, which showed active movements when incubated. In various culture media—such as gelatin, agar agar, etc.—they formed scale-like colonies, which did not liquefy gelatin. Guinea-pigs, rabbits, cats, and dogs, when inoculated with pure cultures, died in a comparatively short time. On post-mortem examination nodular tumors —which are described by Kübasoff as presenting the structure of cancer—were found in various internal organs. He regarded this bacillus as the true cause of the disease.

Schütz (1891), by means of various aniline dyes, was able to discriminate various forms of bacteria in ulcerated cancer of the lip; but these he regarded as mere epiphytes.

Richet (1895) found septic bacteria often present in cutaneous carcinomata; and extracts made from tumors of this kind seemed to possess a special virulence of their own. Thus, while injections of the extract of fresh non-ulcerated cancers had no toxic effect whatever on animals, a few cubic centimetres of the same preparation from an ulcerating cancer caused convulsions and death.

Several investigators have reported the existence of microorganisms in the blood of patients with malignant tumors; and some have claimed for these bodies special etiological significance.

Hayem (1889), however, who has specially studied the various alterations in the form of the blood corpuscles in malignant and other diseases, concludes that the pseudoparasitic bodies are due to degenerative corpuscular changes (microcytosis, poikilocytosis, fragmentation, etc.).

Moty (1894) found micrococci in the blood of nearly all the patients with sarcoma examined *ad hoc* by him. In cultures they developed as a narrow pointed or festooned band, surrounded by small isolated colonies.

Maragliano (1901) examined the blood of thirty-three patients with cancer of various parts of the body. In nine cases bacteria were present—mostly different kinds of staphylococci. In all of these instances the tumors showed some signs of disintegrative processes; but in none of the patients was there any pyrexia or other indication of septic infection. In patients with non-ulcerated tumors he was never able to detect any bacteria in the blood.

The latest champion of the bacterial origin of cancer is Doyen, of Paris, who at a meeting of the French Academy of Medicine, held on December 24th, 1901, announced the discovery of a new "cancer microbe," which he calls *Micrococcus deformans*. He maintains that this microbe—which is a diplococcus—is constantly present in cancerous tumors and may be best demonstrated in sections stained with picric carmine and violet; and that he has been able to isolate it and cultivate it in special gelatin-bouillon media. It presented in pairs and in short chains. He found that cultures were more easily obtained from affected lymph glands and secondary growths than from the primary tumor. He claims to have produced cancerous tumors in various animals by inoculating them with pure cultures of the microbe; and also to have succeeded in preparing a sterilized solution of its toxins—attenuated in a special manner—which when subcutaneously injected into those affected with the disease retards its progress. It is disappointing to find that these exalted claims rest upon nothing more substantial than a "preliminary note," in which the author admits the inconclusiveness of the experiments on which his pretensions are based.

Remarks.—From the foregoing the following conclusions may be drawn:

1. Malignant tumors are singularly prone to bacterial infection, owing to their feeble vitality, which is a consequence of defective sanguinification. The organisms usually present under these circumstances are such as are commonly met with in corresponding normal parts of the body, *e.g.*, micrococci, diplococci, streptococci, various large and small rod-shaped bacilli, etc.

2. In their young and nascent condition non-ulcerated malignant tumors are quite free from bacteria.

3. Although many kinds of bacteria may find a suitable ***habitat*** in malignant tumors, none of these organisms fulfils the requirements necessary for the establishment of their etiological specificity, as "cancer microbes."

Protozoa.

Just as the movement in support of the bacterial origin of malignant tumors was on the wane, a new movement arose ascribing the causation of the disease to parasitic protozoa.

It was thought that it might be due to some other form of parasitic microbe, such as that which produces the coccidiosis of the rabbit's liver, etc.; indeed, this affection became the archetype of all our conceptions of cancer as a protozoan disease. The liver of a diseased animal presents grayish nodules, composed of a thick envelope, enclosing quasi-caseous or fluid contents, which teem with minute bodies, resembling the ova of entozoa—coccidia. The presence of these bodies in the liver causes hyperplasia of the small biliary ducts in their vicinity, with more or less cyst formation and papillary overgrowth; but none of the essential features of malignancy is ever present. Indeed, the animal's health is seldom much impaired. Although the malady is infectious, it is never transmitted by true contagion.

It appears that Pfeiffer, who has specially studied coccidiosis in the rabbit, was one of the earliest to publish an account of parasitic sporozoa in human cancer. On teasing fragments of a malignant melanotic tumor on the warm stage of a powerful microscope, he saw plasmodia in amœboid movement, and observed that they resembled one of the microsporidia which infest cabbages—the *plasmodiphora brassicæ.*

The announcement by Darier in 1889 of the discovery of psorospermial parasites in cases of Paget's disease of the breast, and the finding shortly afterward of similar bodies in cancer cells from various parts of the body, soon made this question the cynosure of pathological eyes, for the secret of the origin of cancer seemed to concentre in it.

Among the earliest supporters of this doctrine were Malassez,

Wickham, Thoma, Sjöbring, Metchnikoff, Soudakevitch, Ruffer, Foà, and Cattle, while their conclusions were disputed by an equally long list of doughty opponents.

The work of these early investigators was entirely histological, and it soon became apparent that they were determined to class as cancer parasites every rounded body that was not obviously either an epithelial cell, a nucleus, a leucocyte, or a red blood globule. Indeed, there were some among them (Pfeiffer, Adamkiewicz, Jackson Clarke, etc.), who went to much greater lengths, maintaining that the constituent elements of cancerous tumors were merely masses of parasitic protozoa, and not epithelial cells as generally believed. In spite of some opposition from the more moderate parasitologists, the investigation was continued in this spirit until Soudakevitch and Ruffer, in 1892, for the first time clearly defined precisely what was meant by the term "cancer parasite." They thus discriminated from the immense variety of so-called parasites certain small rounded endocytes, each of which contained a nucleus, surrounded by voluminous protoplasm, itself circumscribed by a distinct capsule. With the Ehrlich-Biondi stain the nucleus assumed a copper-red color, while the surrounding protoplasm colored light greenish or bluish, the capsule taking a decided reddish tint. Immediately around the nucleus a clear zone was noticeable, and in "parasites" of a certain size fine radial striation was often seen. All bodies different from these, such as had been described by previous observers as cancer parasites, Raffer rejected as such, declaring that they were only pseudoparasites, having no etiological relationship whatever with malignancy.

The precise nature and significance of the bodies thus discriminated still remain to be determined. Shattock and Ballance (1891) were among the earliest of those who undertook experiments, with the object of determining whether cancer could be produced by inoculating animals with psorospermiæ from the rabbit's liver, etc., as the statements of Darier and Wickham implied. Rabbits, monkeys, dogs, and rats were employed for this purpose. The method was to scarify the ear, by making one or more long incisions on its inner aspect; and after bleeding had ceased, to rub into the wounds fresh psorospermial material from the liver of a recently killed rabbit. This was followed by the formation of linear elevations along the incision tracks, owing to reparative hyperplasia, but otherwise the results were always negative. This was the case even when large quantities of psorospermial material were injected into the jugular vein of dogs, etc.

The authors failed to get cultures of these psorospermiæ on any of the ordinary culture media; but the organisms maintained their vitality for considerable periods in fluid rabbit's blood serum prepared by discontinuous sterilization.

They concluded that until animals or human beings had been experimentally infected by inoculation with cultures made from Paget's disease or from cancerous tumors, nothing could be taken as proved as to there being any causal relation between psorospermiæ and cancer.

Delépine (1891) found that the psorospermia-like bodies met with in malignant tumors failed to respond to any of the chemical tests, which give definite reactions with the psorospermial parasites of the rabbit's liver. He also failed to find in the so-called "cancer parasites" any of the developmental forms met with in the parasitic psorospermiæ of rabbits.

By inoculating interlamellar films of water, serum, nutrient gelatin, and other fluids, with psorospermiæ from the rabbit's liver, he obtained cultures of these parasites, and succeeded in following their development through various stages. By this method the changes occurring in individual psorospermiæ could be followed for weeks.

Delépine suggests that the protozoa-like bodies of malignant tumors should be studied in the same way; when, if similar changes were observed in them, the doubts as to their real nature might thus be removed. Attempts subsequently (1893) made in this direction by Delépine and Cooper failed to elicit any indications of multiplication and growth when the so-called cancer parasites were substituted in the experiments for psorospermiæ from the rabbit's liver.

D'Arcy Power (1893), a supporter of the protozoan theory, has also attacked the problem from the experimental standpoint. He brought mucous surfaces of rabbits, rats, etc., that had for some time been kept in a state of chronic irritation, into contact with cancerous tissues, when the former became infected with "cancer bodies," but cancerous tumors could never be thus produced. Only a few experiments were made, and there were no control observations with healthy epithelial instead of cancerous tissues, so that these results are by no means convincing.

In a subsequent publication (1894) Power admits the validity of this criticism, for, he there says, "it may be that the 'cancer bodies' are merely phases in the degeneration of cells. . . . They are met with in normal epithelium which has been slightly irritated; and I am therefore bound to confess myself an unbeliever in any of the 'cancer bodies' which have yet been discovered."

Kurloff (1894) found an organism, which appeared to be identical with *Rhopalocephalus canceromatosus* of Korotneff, in a primary cancer of the skin of the dorsum of the hand of a man aged eighty.

According to Adamkiewicz (1891) the infectivity of cancer is so well established that its parasitic nature may be regarded as a certainty. He maintains that the constituent cells of cancerous tumors are not epithelial cells, as is generally believed, but parasitic organ-

isms. "A cancer cell is not an epithelial cell, but an animal—a protozoön—especially a coccidium (*Coccidium sarcolytes*)." Since all parasitic microbes produce toxins, Adamkiewicz believes that there must also be a special cancer toxin; and this he claims to have discovered in a substance, termed by him *cancroin*, which he has extracted from malignant tumors. He finds that this substance is chemically akin to neurin—"tri-methyl-vinyl-ammonium-hydroxide." By subcutaneous injections of this substance he claims to have cured many cases of cancer after a few weeks' treatment.

This claim he still (1902) maintains; but, it must be stated, that those who have had the best opportunities of closely following his cases have failed to appreciate his alleged curative results; and generally his sensational statements inspire no confidence.

In a further series of experiments (1895) Shattock and Ballance again endeavored to get cultures of the "parasitic protozoa" of human malignant tumors. Under the impression that it might be necessary for the hypothetical parasites to pass through some lower organism in order to acquire infective properties for man and animals, they fed worms, kept in sterilized sand and water, with bits of mammary cancer. These were devoured, but the worms unfortunately died soon afterward, owing to the sterility of the sand depriving them of all other nutriment. Bits of fresh mammary cancers were next buried in garden soil, and six weeks later these were exhumed and introduced into the abdominal cavity of rats; but only negative results ensued. In other experiments, bits of malignant tumors in Petri dishes, etc., were introduced into sterilized sand and water to which a little beef peptone broth had been added, and after variable periods sand from the vicinity of these bits of buried tumor was examined; but although the sand often teemed with amœbæ and bacteria no sporozoa were present. The results of inoculating animals with this sand and with bits of the tumors that had been buried were always negative.

Searching for a protective vaccine against malignant disease, Shattock and Ballance (1895) tried the effect of subcutaneous injections of fifty-per-cent. glycerin extracts of cancer and sarcoma into patients affected with inoperable malignant tumors; but in no case did any improvement ensue.

They next essayed the effect of injections of the fresh serum of animals, such as sheep, which are naturally but little liable to malignant tumors; but these also were inefficacious. The serum of animals into whose circulation cancer juice had been injected was also employed therapeutically, but without any appreciable result.

Juergens (1895) inoculated the peritoneal cavity of rabbits with a magma derived from a metastatic sarcoma. Three months later one of these animals was found to have a tumor in its right eye. On post-

mortem examination a month later a sarcomatous tumor the size of a walnut was found there, the constituent cells of which teemed with oviform coccidia.

In another experiment, a small bit of recently extirpated human melanotic sarcoma was implanted under the conjunctiva of a rabbit's eye, when a fortnight later a melanotic tumor the size of a pea was found to have developed at the seat of implantation.

Microscopical investigations have convinced Juergens that human melanotic sarcoma is due to the presence in the affected part of pigment-producing coccidia; and in the foregoing experiment he claims to have succeeded in transplanting this organism from man to the rabbit.

In another rabbit in which bits of a myxosarcoma of the human ovary were implanted in the peritoneal cavity, tumors were found on the large and small intestines and in the lungs. These tumors contained numerous yellowish-green coccidia-like organisms.

Juergens also inoculated six rabbits in the peritoneal cavity with fragments of melanotic sarcoma from the human pancreas. Within a few weeks each animal was found to have developed melanotic growths. All these artificially produced tumors teemed with ovoid or rounded, brownish-black, pigmentiferous coccidia. Juergens also claims to have inoculated animals successfully with fragments of sarcoma, taken from a patient who had been dead three days.

These cases would be more conclusive if a longer interval had been allowed to elapse after inoculation, so as to insure the subsidence of the local inflammatory reaction, which always follows such experiments and may easily be mistaken for sarcoma. Other experimenters have found that tumor-like swellings of this kind eventually disappear.

With regard to the two experiments in which a few months had elapsed since the inoculation, there are so many fallacies, not easily excluded, to be guarded against (tubercle, mycotic infection, chronic inflammation, spontaneous malignant disease, etc.) that in the face of the overwhelming preponderance of negative results hitherto recorded, these cases cannot be accepted as conclusive evidence of the transmissibility of human malignant disease to animals.

Bosc (1898) endeavored to get cultures of the hypothetical psorosperms of human cancers by incubating bits of recently removed tumors in ordinary culture media. He maintains that the "cancer bodies" multiplied in those media; but as he never even attempted to inoculate animals with these cultures, the value of his statements is comparatively small.

Among those who continued the investigation of the "cancer parasites" discriminated by Ruffer, Plimmer (1899) was one of the first who employed the experimental methods that had been introduced by Sanfelice and the Italian pathologists. He seems to have been so

much impressed by the results of these methods as even to doubt the dictum of Metchnikoff as to the protozoan nature of these bodies.

Although Plimmer managed to demonstrate histologically, to his satisfaction, "cancer parasites" in almost all of the numerous malignant tumors specially examined *ad hoc*, he only once succeeded in isolating by artificial culture "an organism which in certain animals was capable of causing death, with the production of tumors in various parts." His culture medium was an infusion of human cancer prepared, just as the ordinary beef infusion, with the addition, after neutralization, of two per cent. of glucose and one per cent. of tartaric acid.

Guinea-pigs inoculated intraperitoneally with these cultures died in from thirteen to twenty days; and on post-mortem examination the peritoneum, omentum, liver, spleen, intestines, and lungs were found to be studded with small nodules of endothelial structure, the constituent cells of which contained "organisms" similar to those isolated from the human cancer. He claims that these experiments demonstrate "the production of tumors by an organism isolated from human cancer," which, he thinks, "may have a practical bearing on the great question of the etiology of cancer." In some cases he claims thus to have produced by inoculation true malignant epithelial (cancerous) tumors. Thus by scarifying a rabbit's cornea and inoculating it with the sediment of a ten-days-old culture, he found, when the animal was killed forty-eight hours afterward, that free proliferation of the corneal epithelium had taken place, and that these cells were invaded by "cancer parasites." This proliferation spread for some distance. Plimmer seeks to persuade himself and others that this is an artificially produced cancerous lesion. I certainly think he has not brought forward one iota of evidence that will justify such a conclusion. This lesion might just as well have been produced by the inoculation of any irritant. Wyss and others have shown that corneal lesions of all kinds, involving destruction of surface epithelium, are quickly followed by ingrowths of the adjacent epithelial cells.

In numerous other experiments, rabbits and guinea-pigs were inoculated intravenously, intraperitoneally, and subcutaneously, but with merely negative results. In other cases the only obvious effect was that the "organisms" were found post mortem in the blood, internal organs, etc. Nearly three years have now elapsed since the publication of Plimmer's "Preliminary Note"; but, so far as I know, nothing has since appeared in substantiation of his claims.

Pianese (1896) has published a very elaborate study of the histology of cancer, with special reference to the nuclear changes of the morbid cells and to their so-called parasites. He examined specimens from fifty-five cancers of different parts of the body. He describes the mitoses found in cancers, which he classifies. He describes with

special care the group of degenerations which comprise hyalinosis, keratohyatosis, mucoid, colloid, and amyloid changes, and discusses their relations to "les corps de Darier," the sporozoa of Korotneff (*Rhopalocephalus canceromatosus*), and to Russell's bodies.

Attention is then directed to the nucleus and nucleoles of cancer cells. The special nuclear changes may affect chiefly (*a*) the nuclein (swelling, diminution, fragmentation, degeneration); (*b*) the paranuclein (fragmentation, degeneration); or the nucleolus (vacuolization, encapsulation); (*c*) the envelope of the nucleus; or (*d*) the nuclear juice (filamentous nucleoplasmolysis).

In conclusion, he studies (1) hyalinosis of the nucleoplasm; (2) pseudo-adipose or cystic degeneration of the nucleus; (3) amyloid degeneration of the entire cancerous cell; (4) necrosis of the nucleus; and (5) amyloid cancer bodies.

Pianese concludes that up to the date of his communication (1896) we have no evidence, histological or experimental, that would justify us in describing the numerous "parasites" that have been figured and described as being found in cancers, as other than products of alterations of the protoplasm, of the nucleus, or of both combined.

Leyden and Schaudinn (1896), examining ascitic fluid removed from two cancer patients, made the interesting discovery that it teemed with rhizopodia—organisms that had never before been met with in the human body, except as parasites of the gastrointestinal tract. These microbes presented as amœboid bodies, of from 3 to 36 μ in diameter, their shape being globular or irregularly polygonal, and at intervals they emitted processes of hyaline ectoplasm. The pseudopodia of adjacent organisms sometimes anastomosed. Each of them was furnished with a nucleus of the typical rhizopod type, and then multiplied by segmentation or gemmation, colonies often being formed. One of the patients had cancer of the pylorus; the other had an intraabdominal tumor.

When a drop of the ascitic fluid or its centrifugalized sediment was microscopically examined in the fresh state, the organisms were readily seen, as above described. Permanent preparations were also made. As to the possible etiological relation between these rhizopods and the concomitant cancerous disease, the authors decline to commit themselves; but they believe them to be pathogenic. Meanwhile they have modestly named the organism, *Leydenia gemmipara Schaudinn.*"

The foregoing publication has been the starting-point of many recent researches. Thus Nils Sjöbring (1900), with a culture medium consisting of nearly equal parts of sterile fluid and peptone gelatin, to which were added 1.5 per cent. of watery solution of potash soap prepared with human fat, and one per cent. of cane or grape sugar,

succeeded in cultivating from fresh human tumors an animal organism presenting amœboid, rhizopod, and involution forms.

Tubes of this special culture medium were inoculated with pieces of non-ulcerating human tumors that had been aseptically treated; and these were then incubated for a week at 37° C. (98.6° F.). By this means, from various carcinomata, sarcomata, uterine myomata, and ovarian cystomata, Sjöbring succeeded in isolating these rhizopod organisms.

With these cultures he inoculated eight white mice, and in four cases positive results were obtained. In two cases cultures of human mammary cancers, subcutaneously injected, after a period of three months, are alleged to have caused the formation of cylinder-celled cancer of the cutaneous sweat glands and hair follicles. In another experiment the resultant tumor resembled an adenoma of a sweat gland. In the fourth case a culture from a colloid cystoma of the human ovary, intraperitoneally injected, gave rise to colloid cystoma of the epididymis, etc. In all of these animals "cancer bodies," similar to those found in human malignant tumors, were demonstrated. With rabbits and guinea-pigs the inoculations gave only negative results.

In their initial stage these "organisms" presented as sarcous, rounded, quasifatty masses; subsequently pseudoplasmodia developed. In certain forms the nuclear chromatin could be demonstrated by aniline blue staining and with iron-alum-hæmatoxylin. Their development was like that of the amœbosporoids of the protozoa; but sexual conjugation and the sickle-shaped germ were absent.

Histological sections of the artificially produced skin tumors in mice, exhibited at the congress of German surgeons in 1901, produced a by no means favorable impression. The evidence as to epithelial new formation was considered to be inconclusive. Juergens could not recognize the so-called cancer bodies as parasites; and Israel was of the same opinion, maintaining that the so-called sporophoroides and rhizopodia were nothing but fat globules and *débris*.

Max Schüller (1900) has published an account of an organism—of protean form—which he detected in carcinomatous and sarcomatous tumors, and isolated by cultures. His procedure was that of incubating bits of the fresh tumors, taking care not to expose them to a lower temperature than that of the body. He discriminates two typical forms; of these the more characteristic are large organisms, three or four times the size of red blood corpuscles—round or ovoid, refractile, of golden yellow or brownish color, having a well-defined capsule perforated by numerous pores, within which are three or four small protoplasmic masses which, in the course of development, appear to escape through the capsular pores and form independent organisms. It is from the latter that the smaller type of organism is believed to

originate; these present as clear or finely granular, rounded cells of golden color.

In living, hanging-drop cultures, these organisms present fine peripheral processes. It is believed that the small types of organism develop into the larger ones.

Cultures injected into the tissues and organs of rabbits and other animals caused local proliferations similar to those met with in commencing cancer—carcinomatous cultures being capable of producing sarcomatous, etc.

Max Schüller has also found and made cultures of similar organisms from the lesions of acquired and congenital syphilis.

Not a little sensation was caused when, in 1901, Völcker declared that Max Schüller's large, yellow, cancer parasites were in reality nothing but cork cells, from the oil used for the immersion objective. This of course led to recriminations, and a lively controversy is still (1902) going on.

Olt (1900) considers that the so-called parasites of cancer are in reality red blood cells in various stages of degeneration. He attempted to obtain cultures from cancers from the horse, dog, etc., using various media. The results were negative. He concludes: "From the fact that these supposed parasites are iron-containing bodies, and that their optical properties are very similar to those of the red blood cells, it may be inferred that the latter are concerned in their formation."

The latest champion of the "protozoon of cancer" is Gaylord, who claims to have discovered an organism of this kind in ascitic fluid, derived from a patient with colloid cancer of the peritoneum, which, when inoculated into animals, produced cancerous tumors. Cultures of this organism on fucus crispus bouillon gave similar results. He also found microbes of this kind in various cancerous and sarcomatous tumors, and got pure cultures of them. In advanced cases they could always be detected in the patient's blood and in the internal organs. With cultures from these various sources many animals were inoculated; and in a few instances nodular tumors were found, a month or so later, when the animals were killed. In an experiment in which the injection was made into the jugular vein of a guinea-pig a pulmonary nodule was found when the animal was killed three and one-half weeks later. Microscopical examination of this artificially produced tumor revealed proliferous cells in branching columns, which Gaylord interpreted as adenocarcinoma. For the demonstration of this protozoon Gaylord relies chiefly on unstained specimens—the scrapings of cancerous tumors, etc. He found the parasites in every case of cancer and sarcoma specially examined, as well as in myxoma, fibroadenoma, colloid goitre, and syphilitic lymph glands. It is evidently very

similar to the bodies previously described by Schaudinn and Sjöbring, and to Max Schüller's "young forms." In the fresh state Gaylord's parasite closely resembled fatty globules; indeed, it was only by finding that they did not react with ether and osmic acid as fat does that he was able to discriminate them from fatty aggregations. He next found that he could crack their edges with a cover glass. They existed in greatest abundance in the softened disintegrating areas and cancerous tumors, where Plimmer and Ruffer could never find parasites.

Gaylord maintains that there is great resemblance between his cancer parasites and the bodies met with by Pfeiffer and others in variola and vaccina, which are also believed to be protozoa. They present as pale yellowish granular bodies, like fat droplets, from 3 to 10 mm. in diameter, large and small types being discriminated. By incubating hanging-drop preparations of fresh cancer juice derived from scraping the tumor, the smaller forms of the organism could be followed in their development; they augmented in size and became granular, emitting pseudopodia and developing a nucleus, ultimately being converted into sporiferous sacs.

Remarks.—Before entering on any discussion as to the etiological significance of the hypothetical protozoa of malignant tumors, we want to be reasonably assured that such parasites really exist in these tumors. Hence it is to this aspect of the question that we must first of all direct our attention.

It will be gathered from what has been stated that the evidence hitherto adduced is almost entirely histological; for the results of cultures and inoculation experiments, in this connection, have established nothing definite.

Even if pathologists were unanimous in interpreting the appearances revealed on microscopical examination of malignant tumors as indicative of the presence of protozoa, in the absence of corroborative evidence such unanimity would fall far short of scientific proof. But when we find that most pathologists decisively reject this interpretation, maintaining that the bodies which have been thus described are not parasites at all, but merely products of the biological changes, often degenerative, incidental to the life of the part, derivatives of the nuclei or protoplasm of the tumor cells, of leucocytes, of red blood globules, etc., the futility of relying on the appearances revealed by the microscope for the proof of the presence of parasitic protozoa in malignant tumors becomes apparent.

It is passing strange that those who are so insistent on maintaining the protozoan nature of certain appearances revealed by the histological examination of malignant tumors have with singular unanimity failed to make control observations. Had they done so they would

have found similar appearances often present in various non-cancerous conditions, *e.g.*, in variolous and vaccinal lesions (Pfeiffer, Guarnieri, Mann, etc.), in healing wounds, and after artificial irritation (Pierallini, D'Arcy Power, Galeotti, etc.), in syphilitic lesions, herpes, endometritis, mycosis fungoides, etc.

Moreover, in undoubted cases of human psorospermosis, such as those described by Leuckart, Albarran, Keen, Silcock, Eve, and others, the lesions met with bore no resemblance whatever to malignant disease. Similarly in animals (rabbits, etc.) the lesions caused by these parasites never present any of the special features of malignant tumors.

It accords with this that tumor cells containing "parasitic protozoa" always appear to be in a state of degeneration, and to be incapable of that active proliferation which is an essential feature of malignancy.

Again, the chemical reactions of malignant tumors are very different from those of lesions in which psorospermia abound, for they contain neither chitin, cellulose, nor albumose (Brodie, Hewlett). On the other hand, they are rich in glycogen, which, according to Brault, is absent from parasitic pseudoplasms. Moreover, "falciform bodies" have never been demonstrated in the so-called psorospermia of malignant tumors; and no alkaloid has ever been separated from them.

Before such bodies as those described by Schaudinn, Sjöbring, Max Schüller, and Gaylord can be accepted as parasitic protozoa, the possibility of their being derivatives of preëxisting somatic structures must be negatived.

The more carefully the subject is considered, the clearer it appears that the "protozoon of cancer" has failed to make good its entity. This hypothetical microbe appears to be a mere figment of the imagination, that has been projected into the field of observation. In consequence of errors of diagnosis it is a case of mistaken identity.

In this opinion modern zoölogists are at one with pathologists. Thus Doflein, one of the latest investigators of the protozoa, says: "The zoölogist cannot at present admit that any one of the so-called cancer parasites is a protozoon."

Blastomycetes.

The third great movement in connection with the microbic origin of malignant tumors was originated by Russell, who (in 1890) detected certain "fuchsin bodies" in cancerous tumors, which he regarded as the characteristic organisms of cancer; and these he believed to be parasitic blastomycetes of the same order as the yeast fungi. It cannot be said that Russell's views met with much support until some years later, when the Italian pathologists took the matter up, and

by means of experimental methods aroused fresh interest in the subject.

It is especially owing to the work of Sanfelice, director of the Hygienic Institute at Cagliari, that so much attention has centred on the blastomycetes in this connection. Moreover, he removed the study of the question from the histological to the experimental region. It appears that even as early as 1895 he was engaged in studying certain organisms found in infusions of various kinds of fruits; and in so doing he was struck with the resemblance which some of them presented to the so-called "fuchsin bodies" found by Russell in human cancerous neoplasms. Of these organisms he obtained pure cultures, with which he proceeded to inoculate the tissues and organs of various animals. He thus found that some of them were pathogenic, the effect varying in different animals. In many animals nodular swellings were produced at the seat of inoculation, and sometimes in more distant parts, which he thought might not unfairly be compared with human malignant tumors.

Sanfelice has no doubt that the organisms he experimented with were blastomycetes; and the pathogenic form he discriminates as "*Saccharomyces neoformans.*" In most cases the tumors thus produced were nothing but inflammatory pseudoplasms. But with cultures of a microbe of this kind, isolated from a fermenting infusion of lemon skin, he claims to have produced, by inoculation, malignant epithelial neoplasms (cancers) in dogs.

When these cultures were injected into the peritoneal cavity, nodular formations at first resulted; from these fresh cultures were made; and after the microbe had thus been passed through several dogs, it was found to have acquired increased virulence.

Of thirty dogs inoculated with cultures thus produced, in two Sanfelice claims to have caused true epithelial cancer.

In the case of a bitch inoculated in the posterior mammary region, there was considerable tumefaction at the seat of inoculation one month afterward. The animal then became cachectic and died ten months after inoculation. Besides the mammary tumor post-mortem examination revealed enlargements of the adjacent inguinal and abdominal lymph glands. Histologically examined, all of these tumors showed the structure of glandular cancer. Numerous "parasites" were present in them, but no cultures could be obtained. The latter defect is unfortunate, as the possibility of the animal having been previously affected with mammary cancer, to which bitches are prone,* thus cannot be excluded.

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*According to Casper and Schütz four per cent. of all dog's diseases are tumors, half of which are carcinomata, the latter being especially common in elderly dogs.

A similar defect characterizes the other positive result, when the testes were inoculated, and a secondary tumor formed in the penis.

Roncali, investigating the subject chiefly from the histological standpoint, has detected in human cancers and sarcomas intra- and extracellular bodies, similar to those described by Sanfelice. Roncali is convinced that these bodies are parasitic blastomycetes.

With Sanfelice, in 1898, he succeeded in isolating similar organisms from human cancerous tumors, which they found to have pathogenic properties; and when these were injected into certain animals pseudo-inflammatory, tumor-like swellings resulted. These cultures were made with difficulty, and they soon lost their virulence, so that nothing further was accomplished in this direction.

At the meeting of the Italian Surgical Congress in 1900 Roncali again took up this question. He described the appearances found on histological examination of an intracranial fibrosarcoma of the dura mater. This tumor teemed with parasitic blastomycetes. After having fully described their morphological features and their precise localization in the tumor, which were such as clearly indicated genetic correlation, he arrived at the following conclusions: (1) This case proved that blastomycetes could not be mere accidental epiphytes in malignant tumors. (2) Although he failed to isolate and cultivate blastomycetes from the tumor, this was no proof that they did not exist, nor did it imply that they were mere products of degeneration; for, as Sanfelice had shown, when the parasites assumed the form of "Russell's bodies," they were no longer cultivable. (3) Provided one knew how to recognize them, and had the patience to search for them, these parasites could always be found in malignant tumors. (4) The so-called parasitic protozoa and coccidia, described by other investigators as being constantly present in malignant tumors, were nothing but blastomycetes, as the author had maintained ever since 1895. (5) Blastomycetes were the real etiological factor of malignant tumors (cancer and sarcoma), as Sanfelice had experimentally demonstrated.

In the interesting discussion which followed the reading of Roncali's paper, Bastianelli maintained that it was not sufficient to have stained and described these bodies, to prove that they were blastomycetes. It was necessary to give this proof, which the author had not done. Biondi said that of all the researches hitherto made in connection with the parasitic origin of malignant tumors, the only really important facts hitherto obtained were the two positive results announced by Sanfelice, and these undoubtedly gave food for thought.

Durante could not support the blastomycetic theory of the origin of malignant tumors, because the precise conditions which would enable him to say that the blastomycetes were really the causal factor were wanting. Sanfelice's experiments were lacking in this respect. He

had seen his specimens, and was not convinced as to the epithelial nature of the experimentally produced tumors.

Maffici and Sirleo (1896) sum up as follows: (1) On *a priori* grounds the infective origin of malignant tumors is probable. (2) The infective agent has not yet been determined, by either histological or experimental researches. (3) Investigations relating to the infectious agents of tumors should not be limited to one class of parasites. Among the blastomycetes some have pathogenic properties. (5) The lesions induced by blastomycetes are quite different from such new growths as carcinoma and sarcoma. (6) Pathogenic blastomycetes may induce septicæmia, suppuration, and chronic inflammatory changes of granulomatous nature. (7) Blastomycetes found in human malignant tumors, when inoculated into animals, have hitherto produced only ordinary inflammatory pseudoplasms. The authors deny that malignant epithelial tumors can be produced in dogs by pure cultures of blastomycetes, as Sanfelice alleges. (8) In human cancerous and sarcomatous tumors blastomycetes cannot always be demonstrated, either histologically or by cultures. (9) In ulcerating human malignant tumors blastomycetes may be found. (10) The conditions under which this happens and the distribution of the blastomycetes are such as lead to the inference that the infection has been superadded. (11) While not denying the possibility that blastomycetes may cause malignant tumors, the authors maintain that this has not been proved experimentally. The tumor-like swellings produced in animals by inoculation with pure cultures of blastomycetes are inflammatory pseudoplasms (granulomata) and never true malignant tumors.

Corselli and Frisco isolated and obtained pure cultures of blastomycetes from a sarcomatous tumor of the mesenteric glands of man. With these cultures they inoculated guinea-pigs, rabbits, and dogs; and in several of the animals thus experimented on they claim to have produced similar sarcomatous growths.

Even before the Italian pathologists took the matter up, several well-marked instances of blastomycetic infection had been reported.

Thus Busse, in 1895, in a case of suppurating pseudosarcomatous tumor of the tibia, found in the primary as well as in the secondary swellings blastomycetes which were histologically demonstrated. Pure cultures were made, and when rabbits, dogs, etc., were inoculated with these cultures, suppurative local swellings resulted. In white mice these inoculations caused death, and the fungi were demonstrated in the animal's blood.

Kahane also demonstrated and made pure cultures of blastomycetes from cancers of the uterus, etc., and in cases of this kind he claims to have seen similar parasites in the blood.

Curtis, of Lille (1895), has recounted the history of a pseudomyxomatous tumor, with contagious properties, which appeared to be due to blastomycetic infection. Microscopically examined, the tumor consisted of scanty fibrillar tissue, containing crowds of large yeast-like cells, some of which exhibited buds, and all of which reacted to the microchemical tests for cellulose. These cells grew rapidly on potato and gelatin, multiplying by gemmation. The author named this organism *Megalococcus myxoïdes*. He claims to have succeeded in transplanting a fragment of this tumor into a rabbit, in which, in the course of twelve days, it gave rise to a tumor the size of a small orange, which contained the yeast-like fungi in abundance.

Niessen (1894), while examining the blood of a woman with advanced uterine cancer, found in it an organism, which he believed to be the cause of the disease. In this blood a dark green mould developed, which was cultivable. It proved to be an unknown species of organism, intermediate between a mycete and a mould. It grew with great luxuriance in human blood, in sterile diabetic urine, and in water; and the products of the cultures in these different media were themselves so diverse that it was difficult to believe they were derived from the same source. This organism Niessen named *Cancero-myces* or *Cladosporum cancerogenes*.

According to Bra (1899) the specific cancer microbe is an "ascomyces," which he has found in the morbid tissues and in the blood. By culture methods he has succeeded in isolating this organism from a large number of tumors, *e.g.*, cancers of the ovary, breast, uterus, etc., as well as from sarcomata of the maxilla and parotid. He has employed two methods—insemination of portions of the tumors and inoculations from the blood of affected persons. The medium used was cow's udder bouillon, and the culture appeared as a scum and a sediment after from five to eight days' incubation at 86° to 95° F. The organism is of spheroidal or cylindrical form, and multiplies chiefly by sporulation, mycelia being formed. In dogs and rabbits inoculated subcutaneously with these cultures tumor-like swellings were produced, which histologically resembled malignant tumors—cancers and sarcomata. By inoculating a bitch in the mammary region, Bra claims thus to have produced typical mammary carcinoma. From these artificially produced tumors pure cultures were made which contained organisms just like those found in the original tumor. The inoculations into guinea-pigs proved inert.

Curtis, of Lille (1899), who repeated Bra's experiments, declares that, after having taken precautions to eliminate extraneous organisms and other sources of error, neither cultures nor inoculation results could be obtained. He found that all tumors, even when not ulcerated and not contiguous to a free surface, nevertheless teemed with

microbes; while ulcerated tumors simply swarmed with innumerable kinds of microbic life. He concludes that human cancers are neither cultivable nor inocuable; and that experiments hitherto published to the contrary are due to errors of technique, etc.

Buchanan (1899) in many histological researches embracing tumors from different parts of the body, found "the parasites" only in cancerous processes. The appearances revealed were more consistent with these bodies being organisms than forms of cell degeneration. He discussed the rival blastomycetic and protozoan views as to the nature of these bodies, and concluded that it would be best to leave the question of their classification open for the present. He held that in cancer there were to be found bodies foreign to the normal tissues, which there were good reasons for regarding as living entities from without; and that they were a cause, if not the sole cause, of cancer.

Monsarrat (1900) claims to have isolated an organism from cancer, grown it in various media, and to have inoculated animals with pure cultures of it, causing in them endotheliomatous new growths, whence the parasites were recovered. These bodies were identical with the blastomycetes described by Sanfelice. Cultures were difficult to obtain, for of twenty-seven mammary cancers systematically examined only one yielded a positive result. The organism grew but slowly on ordinary media. In six cases he examined the blood of patients with advanced cancer, but in all the results were negative.

He recommends the following technique for the recognition of the organism in cancers: Stain in carmine (lithium carbonate by preference) for twenty-four hours; then for two minutes in one-per-cent. watery solution of methyl violet; then place in picric acid for another two minutes; dry with filter paper and decolorize with clove oil. The organisms are violet, the tissues taking the picrocarmine double stain.

Experiments on animals were made and endotheliomatous nodules were produced in the peritoneum, liver, lungs, kidneys, etc.

Monsarrat's cultures soon lost their virulence and became inert. Attempts to sustain or increase their pathogenic properties by successive passage through guinea-pigs and other animals were unsuccessful.

Leopold (1900) found blastomycetes in non-ulcerated cancers from different parts of the body. Of twenty such tumors examined he obtained cultures from four. His best material was derived from the ovarian cancers. A special feature of his work is the prolonged study he made of particles of cancer substance in hanging drops of sterile bouillon in a specially constructed thermostatic microscope. In these preparations, some of which were preserved for two hundred days or more, blastomycetes were seen in various stages of development, and their multiplication by budding was studied. The organisms isolated from all of these four cancers caused glucose to undergo alcoholic

fermentation. In fixed preparations double-contoured and budding organisms, as well as round bodies, were found, and there could be no doubt as to their being blastomycetes. The following experiments on animals were made: (1) A small piece of fresh human cancer was implanted into the abdomen of a rabbit, with aseptic precautions. On the death of the animal, four years and five months afterward, there was found new a typical epithelial overgrowth in the lung. (2) Fresh cancer substance implanted into the abdomen of a rat was followed by death, with the production of "adenosarcoma" in the right groin. (3) A pure culture from cancer of the human ovary, injected into the testis of a rat, caused multiple sarcomata (myeloid and round-celled) to form in the abdomen.

In all the human material new blastomycetes were present; the same organisms were also found in the experimentally produced tumors; and from the latter pure cultures were again secured. A curious feature of Leopold's experiments was the production of sarcomata in animals, with organisms derived from human cancers.

Of fifteen human malignant tumors removed with the strictest aseptic precautions, and examined for blastomycetes, Carini (1900) got only one successful culture. This, he thought, was probably a contamination product. He never succeeded in producing a malignant tumor by the injection of pure cultures into animals. Histological examination of forty-four human tumors (mostly malignant) showed the presence of "Russell's bodies" in eighteen. Similar bodies were found in non-malignant tumors, and even in normal structures, such as the prostate. He considered that the staining reactions of these bodies were not really characteristic of blastomycetes.

Borrel (1901), studying the minute anatomy of the testis and spermatogenesis in guinea-pigs, found that the cells concerned in the formation of spermatozoa exhibited, at an early stage of the process, an attraction sphere or archoplasm, which had characters identical with those of the cell inclusions of cancer. Borrel considers that at the present time there is a tendency, when studying the histology of cancer, to range everything that is round and possesses a capsule among the blastomycetes; and this he regards as unjustifiable.

The yeasts isolated by cultivations from cancerous tumors he ascribes to contaminations; and the results obtained by inoculation experiments are inconclusive.

Sternberg (1899), using Sanfelice's methods, examined a large number of human cancers, but failed to detect any parasites. He found nothing but cell degeneration products.

Nichols (1900) often found bodies in human malignant tumors like those described by Sanfelice; but of many inoculation experiments only three gave positive results. In these cases the nodular swellings

produced were granulomatous, and had not the least resemblance to human cancer.

Petersen and Exner (1899), experimenting with Sanfelice's *Saccharomyces neoformans* and other blastomycetes, conclude that only a few of the endocytes found in malignant tumors can be interpreted as parasites. Cultures of yeasts from malignant tumors so seldom occur that the few successful results may be ascribed to accidental contamination. Those animal and human diseases that have been recognized with certainty as due to yeast infection (cutaneous ulcers, inflammatory swellings, endometritis, abscesses, etc.) have no resemblance whatever to cancer. The tumor-like lesions produced by yeast inoculations are granulomata and not true tumors.

Wlaeff and Weinberg (1899) repeated Sanfelice's inoculation experiments, but failed to produce any tumor having the least resemblance to cancer or sarcoma. As a rule, only granulomatous swellings resulted; but in a few cases pseudadenomatous, cyst-like, and papilliferous formations followed. Wlaeff was able to exalt the virulence of pathogenic blastomycetes by repeated passage through animals. Cultures thus treated produced different results when inoculated into various animals; in some they caused septicæmia, in others local swellings and cysts, and in guinea-pigs a cutaneous lesion like lupus vulgaris. Weinberg found that the cysts produced by this injection of feebly virulent cultures contained numerous more or less degenerate blastomycetes, the cyst wall being of inflammatory origin. Wlaeff isolated blastomycetes from the juice of a sarcoma of the human uterus and obtained pure cultures of them. He also demonstrated their presence histologically in the tumor.

In a subsequent publication (1901) Wlaeff concludes that, since numerous investigators have isolated blastomycetes in pure cultures from malignant tumors, and have by inoculation with these produced infective growths in animals, these organisms are the causative agents of malignant disease. He prepared a serum for inoculating animals against the disease, and found that in rats and monkeys it conferred protection against growths caused by blastomycetes. Wlaeff subsequently used this serum for the treatment of sixty cases of human malignant tumors, and came to the conclusion, that when it was injected early, before lymph-gland dissemination had supervened, it had a curative effect. The serum employed was obtained from the blood of asses and geese that had previously undergone a series of inoculations with blastomycetic cultures.

Shchiwan (1899), recognizing the existence of blastomycetes in animal bodies, has proceeded to study their fate under these circumstances. Working with *Saccharomyces subcutaneus tumefaciens* of Curtis, and other yeasts, he concluded that the destruction of pathogenic as

well as of non-pathogenic blastomycetes is effected by the digestive powers of leucocytes, which take up the living organisms and destroy them (phagocytosis). Shchiwan claims to have seen yeasts multiply by budding within the phagocytes. He concludes that the destruction of yeasts within the organism takes place in accordance with the general laws of phagocytosis. The capsule, which sometimes forms round blastomycetes embedded in the tissues, he regards as a defensive arrangement by the organism against the further spread of the parasites.

Podvyssotski (1900) struck out a new line by experimenting with an organism parasitic on cabbages (*Plasmodiaphora brassicæ*) and other plants, which is a kind of myxomyces. He inoculated rabbits, guinea-pigs, etc., with these parasites, producing granulomatous formations—"myxomycetic perithelioma." Within the cells of these artificially produced tumors he found spores of the plasmodiaphora; in such vicinities there were also many giant cells and evidences of phagocytosis. These nodular formations were evanescent.

Gilchrist in 1896 described a case of skin disease ("blastomycetic dermatitis") in man, in which the lesion teemed with blastomycetes, which were seen multiplying by budding. He considers that most of the so-called parasites in certain skin affections are merely products of nuclear and protoplasmic changes of epithelial cells and not organisms. Since formations of this kind are found in simple skin diseases, as well as in cancers, they can have no specific causal relation to malignancy.

Gilchrist and Stokes have since reported another example of human blastomycetic infection. In this case the patient was a man, aged thirty-three, with a cutaneous disease like lupus vulgaris. It began eleven and one-half years previously as a pustular pimple on the back of his left ear. Thence the morbid process spread slowly over the face, the older parts cicatrizing. A similar lesion formed, soon after the initial outbreak, on the back of his hand; but this healed after treatment with caustic, about four years after its first appearance. Six months later a third lesion appeared on the scrotum, which spread for a year, and then healed spontaneously. Other lesions formed on the left thigh, back of the neck, etc., and likewise healed spontaneously after some time. There was no enlargement of the adjacent lymph glands, and the patient's health remained good. There was no history of tubercle or syphilis.

Sections of the cutaneous lesions on microscopical examination showed numerous budding blastomycetes, in association with which were many almost typical tubercles. The organisms were mostly extracellular, comparatively few being included in the giant cells. Pure cultures were obtained from the lesion, and grew well on potato

and beer-wort agar. The cultures showed both budding forms and mycelium, although the latter was not met with in the lesion. A horse, a sheep, dogs, and guinea-pigs were successfully inoculated, nodules forming which resembled tumors, especially in the lungs. Since the parasite did not ferment sugar and produced mycelium in cultures, it might belong to the blastomycetes or oïdia. The authors suggest that all quasituberculous lesions of the skin should be searched for similar organisms, which can easily be done by soaking unstained sections in liquor potassæ, when the organisms may be recognized under the microscope as doubly contoured refractive bodies.

A considerable number of somewhat similar cases have since been recorded, in some of which the lesions were very like those of ulcerated cutaneous cancer. Owens, Eisendrath, and Ready (1899) have described an instance of this kind.

Hyde, Hektoen, and Bevan have reported the case of a man, aged fifty-six, with a peculiar form of skin disease caused by blastomycetes. It began four years previously as a raised red tubercle, which gradually extended until, when it had attained considerable size, it was removed by operation. A warty outgrowth then appeared on his hand. A year later this was extirpated, and examined by Hektoen. Sections under the microscope showed blastomycetes; and in cultures mycelium appeared. Rats and mice subcutaneously inoculated died in a few days; and similar organisms were found in the lesions as in the inoculation sites. A striking feature of the histological sections was the epidermoidal hyperplasia and its branching ingrowths. In the vicinity were numerous small aggregations of leucocytes and miliary abscesses, and in these localities giant cells were plentiful.

Similar cases have been reported in man by Wells, Hessler, and others, while Tokishige has met with the disease in horses.

Hektoen, while admitting the blastomycetic nature of some of the intracellular bodies found in human malignant tumors, denies that the local swellings produced by their inoculation are true tumors; they have neither the histological nor the clinical characters of cancer or sarcoma.

Foulerton (1899) has made inoculation experiments in animals with various pathogenic yeasts. In most cases these caused death in from a few days to a few weeks. In many instances granulomatous swellings formed at the site of inoculation; and from these the yeasts were again cultivated. He concludes that "considerably more evidence than is now available must be brought forward before we can form any opinion as to whether Russell's fuchsin bodies, etc., are merely parts of the cancer cells themselves, or whether they are of the nature of animal or vegetable parasites." It is not improbable that some tumors now classed as sarcomata may really be due to yeast

infection; but "as to the exact causation of carcinoma we are still absolutely ignorant."

Klein (1901), having discovered a pathogenic yeast in some ordinary country milk, found that when inoculated subcutaneously into guinea-pigs it produced tumor-like swellings at the seat of inoculation. When the animals were killed some weeks later, the tumors were found to be crowded with yeast cells. Other guinea-pigs were inoculated with the juice of these tumors and with subcultures, with the result that similar tumors again formed, and death sometimes resulted. In the latter cases yeast cells were found in the blood. This yeast seemed to belong to the same group as the blastomycetes of Sanfelice.

In concluding this section on the blastomycetes and their supposed relation to tumor formation, attention ought to be called to De Backer's work in this direction. De Backer approached the subject from a totally different standpoint to that adopted by any of those whose work I have previously referred to. He thought that by the introduction of blastomycetes into the body an artificial phagocytosis might be set up by which any pathological microbes that were present would be destroyed. Assuming that cancer was a germ disease, he proposed to treat it and other germ diseases such as tuberculosis, diphtheria, typhoid fever, etc., by the injection of pure cultures of yeasts.

It appears that the phagocytic properties of the saccharomycetes and some other organisms was known to Bruhat and De Backer as far back as 1892. During microscopical examination of some wine that had gone wrong, Bruhat noticed that some of the cells of the ferment (*Saccharomyces pastorianus*) had included in them other cells, viz., those of *Bacillus aceti*. The two observers then instituted a series of experiments for the elucidation of this phenomenon. They found that young cells of most kinds of saccharomyces were very energetic phagocytes for all kinds of bacteria, englobing and digesting them. From this it seemed to follow, if Metchnikoff's theory of immunity were correct, that organisms of this kind, injected into the blood of animals infected with pathogenic microbes, would greatly assist the leucocytes in their phagocytic work, provided that they could exist in the blood and tissues of their host, without producing ill effects.

To test the practicability of this method guinea-pigs and other animals were inoculated with the ordinary yeasts of commerce; but the results were not encouraging, for owing to the presence of impurities the yeasts often proved pathogenic, causing abscesses, etc. Pure cultures of *Saccharomyces cerevisiæ*, injected with aseptic precautions, were therefore substituted, and these proved innocuous. The animals were next injected with pure cultures, mixed with sterilized fermentable matter; and experiments were made which showed that under these circumstances fermentative changes occurred within the body of

the animals experimented upon, which were none the worse for it. Animals infected with bacterial diseases were next treated in the same way. Guinea-pigs infected with tuberculosis and diphtheria recovered under this treatment. The plan was then tried on man. Bruhat, offering himself for experimentation, was injected in the flank. At the end of five hours a chill occurred, followed by sweating and symptoms of mild intoxication. At the end of three days the reaction had quite ceased, and no harm resulted. The injection caused leucocytosis. Phthisical patients were next inoculated, and it is claimed that in early cases the disease was nearly always arrested; and most other cases improved, the main condition for success being that the cultures inoculated shall be absolutely pure.

In the treatment of malignant tumors, De Backer claims with this method to have achieved astonishing results. Out of sixty cases there were eighteen cures, lasting over some years; and in many others the progress of the disease was markedly retarded.

Here it may be mentioned that, nearly a quarter of a century ago, Pasteur demonstrated that the saccharomycetes could obtain every requisite for their growth in the human body, except that their main food, sugar, could be obtained only in small quantities. This deficiency explains the slow growth of these organisms in normal animal bodies, as compared with their rapid growth in sugar-containing media.

To explain the curative effects of these injections in malignant tumors, De Backer makes use of this hint. He noticed that many of his guinea-pigs, which had lived together in full liberty, while subjected to a long course of pure yeast injections, got very fat and at the same time became sterile; so that even when occasionally impregnation did occur, the fœtus failed to develop. He conceived that this sterility was due to diminished production of glycogenous material in the uterus, etc., consequent on yeast injections. It is known that localities specially prone to cancer, such as the uterus, breast, liver, stomach, etc., are normally rich in glycogen; and as Brault and others have shown, all malignant tumors are also remarkably rich in this material, which is said to be absent from granulomatous inflammatory new formations. Moreover, we now know that the blood of cancer patients is also unusually rich in sugar-forming substances.

With these points in view, De Backer concluded that blastomycetes artificially introduced into the body by using up its glycogen for their own growth, would check the pathological increase of this substance, and so starve the young cancer cells by depriving them of their essential nutriment. Thus the whole tumor would shrink; for, as Brault had shown, the rapidity of the increase of malignant tumors was directly proportional to the amount of glycogen they contained.

In this connection it is interesting to note that of late many in-

stances of the association of malignant tumors with diabetes have been reported (Kappler, Kreutzmann, Tuffier, and others); and most of those who have specially studied this subject maintain that the diabetic state favors the development of malignant disease.

Remarks.—Amid the hubbub of conflicting statements as to the relation of blastomycetes and malignant tumors, we may, I think, discriminate the following propositions:

1. Certain blastomycetes are pathogenic for man and animals, and they may even cause in them lesions which in their gross features somewhat resemble malignant disease. Thus instances of pseudo-sarcomatous tumors, due to the presence of organisms of this kind, have been reported by Curtis, Busse, etc., while quasicancerous lesions of similar origin have been met with by Gilchrist, Owens, Hyde, Hektoen, and others. It also appears that certain oïdia (Obici, Ricketts), aspergilli (Rénon, Saxer, Boyce, Rothwell), botryomycetes (Delore, Poncet), and probably other organisms, may originate similar morbid conditions.

That tumor-like swellings, which are often confounded with sarcomata, may be caused by actinomycotic infection, is now generally admitted by pathologists. Moreover, tumors of this kind are not particularly rare, and they have been seen in almost every part of the body. As Wolff and Israël have shown, pure cultures of these organisms injected into rabbits, give rise to tumor-like swellings.

When carefully examined, these mycotic pseudoplasms are found to differ markedly from true malignant tumors, both structurally and in their clinical features; and they should evidently be classed with the infective granulomata.

In consequence of these important discoveries certain anomalous pseudomalignant lesions, which have long puzzled pathologists and clinicians, may now be moved from the category of malignant neoplasms into that of the mycotic infections.

2. So many pathologists have now succeeded in obtaining pure cultures of blastomycetes from human malignant tumors, that I regard the liability of the latter to blastomycetic infection as having been proved beyond dispute, although not a few investigators have failed to get positive results. Considering the richness of these tumors in sugar-forming materials, which are so favorable to the growth of blastomycetes, it would indeed be strange if they were not more prone to this kind of infection than the normal tissues of the body.

3. In their young and nascent condition it has been repeatedly demontrated, notwithstanding many assertions to the contrary, that non-ulcerated malignant tumors are quite free from blastomycetes.

4. The repeated failures to produce malignant tumors in animals by inoculation experiments with cultures of blastomcyetes prove that

the latter cannot be the specific causative factor of malignant disease. The few instances in which it is alleged that malignant tumors have been thus caused (Sanfelice, Plimmer, Bra, Leopoldi, etc.) are capable of being otherwise explained (blastomycetic or other granulomata, spontaneously arising malignant disease, etc.). The ensemble of many experiments clearly shows that yeast organisms are incapable of causing the formation of true malignant neoplasms (carcinoma and sarcoma).

Contagion and Infection.

Cancer was regarded by John Hunter as due to the action of a morbid poison, which he believed either arose spontaneously or was derived from the contagion of similar disease. He compared it with smallpox, syphilis, tubercle, etc. Hunter's views were therefore similar to those of the modern microbists.

I suppose it was owing to the lead thus given that the now forgotten "Society for Investigating the Nature and Cure of Cancer," which was founded in London at the beginning of the nineteenth century, and which included among its members such well-known men as Baillie, Willan, Home, Abernethy, and Denman, propounded this question among others, "Is there any proof that the disease is contagious?" to which, as to their other queries, only nebulous answers were returned; so that to-day, after a century's interval, we are still asking the very same questions. Indeed, even before Hunter's day, the possibility of the disease being contagious had from time to time been mooted for several centuries.

Contagion as between Human Beings.

With the object of demonstrating the microbic nature of the disease, many attempts have lately been made to show that cancer is a contagious malady. Supposed examples of the transmission of the disease from one human being directly to another have been cited by Bose, Budd, Guelliot, Guermonprez, and others; but the evidence adduced as to contagion in these cases is of such a flimsy and unreliable nature as to be unworthy of detailed refutation.

On the other hand, there is very strong evidence as to the non-contagiousness of the disease between man and man, which I will now proceed to mention.

The attempts made at the Hôpital St. Louis, early in the last century, by Alibert, Biett, and others, to inoculate themselves and their pupils with the disease, were uniformly unsuccessful.

There is not a single well-authenticated case on record of a surgeon having acquired cancer during the performance of an operation for its removal, notwithstanding the frequency of exposure to contagion

under such circumstances. Of the thousands of persons habitually engaged in attendance upon the victims of this disease, how few have ever become similarly affected? Although men have constantly had sexual intercourse with women the subjects of uterine cancer, there is not a single well-authenticated case on record of cancer of the penis acquired in this way. The number of cases in which cancerous disease of the uterus and penis have coexisted in husband and wife is so small as to deprive them of all value as evidence of contagion, only about a score of such concomitances having been published. Yet the frequency of exposure to the risk of contagion is so great that Noble had no difficulty in collecting records of one hundred and sixty-six cases of pregnancy complicating uterine cancer, reported during the ten years 1886–95. During the early stages of uterine cancer sexual desire is undoubtedly increased. Thus may we account for the remarkable series of cases reported by Cohnstein, in which more than a single pregnancy was known to have taken place during the course of the evolution of uterine cancer. I also know of instances of pregnancy occurring after amputation of the cancerous cervix and after curettage for the same. Yet in spite of all this, of one hundred and thirty-four men with cancer of the penis, tabulated by Demarquay, only one had a wife with uterine cancer.

Again, the children of cancerous mothers have never been known to have acquired the disease, even when the placenta, uterus, or other parts of the genital tract had been the seat of the malady. Moreover, mothers with cancer of the breast have often suckled their infants with the diseased organ, yet no child thus suckled has ever acquired the disease. Thus there is every reason to believe that cancer cannot be directly transmitted from one human being to another; in fact, it is essentially a non-contagious malady.

Of course the mere absence of contagion does not of itself absolutely negative the parasitic nature of the disease, for miasmatic maladies, although non-contagious, are none the less due to parasitic microbes; moreover the coccidial disease of rabbits is also untransmissible by true contagion.

Contagion from Human Beings to Animals.

Of the numerous attempts that have from time to time been made to transmit malignant neoplastic disease experimentally from human beings to the lower animals, whether by grafting, inoculation with the juice, magma, etc., by intravenous injection and other ingenious methods, the results have almost invariably been negative.

Among the earliest experimenters Dupuytren fed dogs and other animals for considerable periods with human malignant tumors, but they did not acquire the disease; the dogs that Alibert caused to swal-

low the discharge from cancerous ulcers, etc., experienced similar immunity.

Only Langenbeck, Follin, Goujon, and C. O. Weber claimed each a single positive result. Langenbeck and Follin injected the juice of a malignant tumor into animals, which after they were killed showed nodules with cells corresponding to the original tumor cells. One dog was killed sixty-three days, and the other fourteen days after the injection.

Virchow, Vogel, Wyss, and Billroth made many similar experiments, not killing the animals until several months after the injection, when no trace of any nodules in internal organs, etc., could be found. These experiments indicate that Langenbeck's and Follin's nodules were probably nothing but consolidating inflammatory lesions, around emboli artificially produced by the intravenous injections.

Boinet (1894) inoculated a series of forty rats intraperitoneally with fresh human cancer, and a month later one of these animals became paraplegic and died a few days afterward. On post-mortem examination it was found to have cancer of the liver and spine. The results in the other cases were negative; as also were those of fifty subcutaneous inoculations.

Mayet (1893) claims to have successfully transmitted the disease to a white rat by repeated subcutaneous injections of a filtered glycerin extract of human cancer. Eleven months after the injections two pea-sized cancerous nodules were found on the surface of the animal's kidney. Six other inoculations yielded only negative results.

In like manner Francotte and De Rechter (1892) claim to have transmitted human cancer to a white mouse.

Dubois (1897) injected animals subcutaneously with material obtained by harpooning fragments of human cancers and mashing them up. As a result tumor-like swellings formed in several of the animals thus experimented upon.

Having in view the immense preponderance of negative results and the many sources of fallacy, we are forced to regard these alleged successes with great reserve.

Richet and Hericourt (1895), believing that malignant tumors were caused by a specific microbe, made experiments with the object of discovering a prophylactic or curative serum against it. Having taken a recently removed sarcoma of the bones of the leg, the tumor was crushed and triturated with water, the resulting solution being filtered. This fluid was then injected into the circulation of a donkey and two dogs, causing no specially obvious reaction. At periods of from five to fifteen days later these animals were bled, and the separated serum was used for treating patients with malignant tumors, about 3 c.c. of it being injected daily into the tissues in the vicinity

of the tumor. In several cases temporary local improvement followed, but no cures have been substantiated. Very numerous experiments of this kind have been made.

Instead of using the serum of animals that have been inoculated with cancer or sarcoma products, Arnozan, Arloing, and others have employed instead the serum of animals, such as donkeys, which have naturally but little tendency to malignant tumors. The results of this method have been similar to those following the use of "cancer serum." These experiments seem to contraindicate the existence of a specific virus in malignant tumors.

In like manner Shattock and Ballance (1896), seeking for a protective serum against cancer, tried the effects of subcutaneous injections of a fifty-per-cent. glycerin extract of cancer and of sarcoma on patients affected with malignant disease. In one case over fifty of these injections were used, but no reaction ensued and there was no retardation of the progress of the local disease. Sheep serum was equally inefficacious; as also was the serum of various animals into whose circulation the juice of malignant tumors had been injected.

Contagion as between Animals of the Same Species.

It is reasonable to suppose that inoculation experiments would have a better chance of success if confined to animals of the same species; but in this direction also nearly all the experiments have proved abortive. Hanan and Eiselsberg, Moran, Mathis, Wehr, B. Smith, and Washbourn now allege that after numerous failures they have at length succeeded; but their results are open to just such fallacies as those previously mentioned.

It appears that dogs are liable to have certain venereal growths form on the mucous surfaces of the external genitalia, which often spread from animal to animal during sexual congress, but which cannot be transferred to any other animals except dogs. They seem to present none of the really essential features of malignancy. From the histological appearances the disease has been variously diagnosed by pathologists as inflammatory, as cancerous, and as sarcomatous. Its real nature has yet to be determined. It can be transmitted artificially as well as *per vias naturales*.

Both the naturally arising and the artificially produced growths are apt to abort suddenly. The disease may be of parasitic origin, although this does not necessarily follow from the fact of its being transmissible, for the contagious agent may be the epithelial cells themselves. Thus O. Lanz has lately succeeded in experimentally producing ordinary warts by subcutaneously inoculating finely chopped-up warts from the patient's hands, although all attempts to isolate organisms by culture from these warts failed. Similarly non-malignant

papilliferous parovarian tumors are often transmitted in this way across the peritoneal cavity.

B. Smith and Washbourn (1898) transplanted small fragments of these contagious growths of dogs just mentioned, immediately after their removal from one animal, under the skin of another, with positive results in thirteen out of seventeen animals experimented on. Some dogs were found to be immune. Serial transplantations were also successfully effected; but in these there was no evidence of increase in virulence. The maximum of growth was attained three months after inoculation, after which they began to retrograde and finally completely disappeared. Very rarely secondary pseudoplasms are said to have appeared in the lymph glands and sometimes even in internal organs.

In the present state of knowledge it is impossible to admit that this disease—whatever its precise nature may ultimately prove to be—has any similitude to human cancer or sarcoma.

Thus attempts to establish the contagiousness of malignant tumors have entirely failed; therefore we must answer the question, "Is cancer contagious?" with a decided negative.

Autoinoculability.

The evidence as to autoinoculability of carcinoma and sarcoma is far more cogent and weighty than any that has hitherto been adduced in support of the contagiousness of these maladies. But as nothing new has lately been adduced in this connection, I must refer the reader to my articles in Vol. XVII. of the TWENTIETH CENTURY PRACTICE OF MEDICINE (pp. 212 and 488) for a summary of our knowledge on this subject. Here it must suffice for me to mention that the phenomena met with more closely resemble those of tissue grafting than they do those resulting from the inoculation of contagious disease. It may be inferred that the constituent tumor cells are themselves the agents for spreading the disease, and that the autoinoculability of malignant neoplasms is a phenomenon of the same order as their metastasis. Here, as before, there is no evidence of the existence of a specific cancer microbe.

Infection.

Malignant tumors are of much commoner occurrence in some parts of the world than in others, the maximum of frequency being in prosperous European communities, such as France, England, etc.; whereas in tropical and arctic regions the disease is believed to be very rare. In every country its incidence presents many topographical variations; and lately attempts have been made to utilize these irregularities as evidence of the infectious nature of the disease, which, it is alleged,

may manifest epidemic, endemic, and even pandemic characters. Hence we now often hear of "cancer districts," "cancer houses," and even of "cancer rooms." It is alleged that malignant disease is prone to occur in damp, low-lying situations, in the vicinity of sluggish streams, in marshy areas, in localities prone to floods, in sewage-saturated regions, in places having a retentive subsoil, such as clay, in the vicinity of trees, etc.; and that its infection is spread by water, uncooked vegetables, insects, animals, etc.

Haviland's statistical researches seem to indicate that in England the cancer mortality varies according to the local geological and topographical configuration and its consequences. He maintains that the regions of highest cancer mortality are low-lying districts, traversed by or contiguous to rivers, that seasonally flood the adjacent riparial lands, and that have retentive subsoils, consisting of alluvial deposits or clays. On the other hand, he finds that high and dry sites, where the drainage is good, where floods do not occur, and where the subsoil consists of hard, non-retentive rocks (such as in the English lake district), or of absorbent substances like chalk and oölite, have the lowest mortality from malignant disease. The registrar-general's statistical reports also show that certain districts which are flat, low-lying, and marshy have exceptionally high cancer death rates.

Nevertheless, I am unable to accept Haviland's conclusions as a sufficient explanation of the topographical variations in the distribution of the disease; for all low-lying and seasonally flooded districts have not a high cancer mortality, and all high, dry, and rocky sites do not enjoy comparative immunity. Moreover, many islands that have no rivers, that are not low-lying, and that are not of alluvial or clay formation, nevertheless have a very high cancer mortality, *e.g.*, the rocky Scilly and Channel Islands, and the Isle of Wight.

It appears to me that the conditions of life peculiar to the respective populations are of more importance in determining the incidence of malignant disease than any features in the geological and physical configuration of localities, although it is probable that the latter play a part—if only an indirect one.

It accords with this that the cancer mortality is generally lowest where the struggle for existence is hardest, the density of population greatest, the tubercle mortality highest, the average duration of life shortest, the infantile and general mortality highest, and where sanitation is least perfect—in short, among the industrial classes of our large towns; whereas, among the wealthy and well-to-do, where the standard of health is at its best and life is easiest, there the cancer mortality is highest. A striking example of this is the town of Bath, where the local incidence of cancer has been carefully studied by Symons, as I shall presently have occasion to relate.

Scott (1900), after studying the prevalence of cancer in the Chelmsford and Malden districts of Essex, concludes that whatever truth may underlie Haviland's theory, it is insufficient to explain the distribution of cancer in these parts. Essex is a flat, marshy county, with a clayey subsoil, and it used to be the home of malaria; yet the cancer death rate for the county is by no means high, being below the average for England as a whole. Although the unions of Chelmsford and Malden contain an excessive proportion of marshy land and estuary ("saltings"), yet their cancer death rate is less than that of the whole county. Those parts of the two unions which include the greatest extent of muddy foreshore, creek, and "saltings" have a smaller cancer mortality than that of the whole of the two unions taken together. The disease was found not to be specially prevalent in places situated on the banks of the fresh-water rivers. In these parts of Essex, therefore, the cancer mortality bears no evident relation to the variations in the physical features of the country.

The first deliberate attempt to utilize topographical irregularities in the distribution of malignant disease, as evidence of its infectious nature, seems to have been made by Arnaudet (1889). In certain remote rural districts in Normandy he found that malignant tumors were two or three times more prevalent than in Paris, where the disease is of great frequency. He also adduced instances of cancers coexisting in various organs of persons living in certain houses or in their vicinity. Hence he concluded that the locality where a cancer patient had lived was contaminated; and he thought it probable that the contagion was spread chiefly through drinking polluted pond water, which also contaminated the local cider, etc. Similar instances were soon afterward advanced by Sorel, Guelliot, Fabre, Fiessinger, Webb, D'Arcy Power, and others.

In support of the infectious nature of the disease it was alleged that the dwellers in certain houses, and even in certain rooms, became affected with cancer, either simultaneously or successively, with undue frequency; that instances of the disease attacking two persons living together (*cancer à deux*) were relatively frequent; and that in certain localities so many cases might be met with as to constitute an epidemic.

Fiessinger (1893) has met with several examples of such outbreaks. He believes that these "epidemics" are particularly apt to occur on the banks of rivers, at the borders of woods, etc., and he suggests that insects, which are plentiful in such places, are concerned in disseminating the disease, as well as contaminated fingers, etc.

Guelliot, of Reims (1894), has reported forty cases in which malignant disease appeared to have been spread by contagion. He claims to have proved: (1) that malignant disease is unequally distributed

in adjoining districts in such a manner that neither heredity nor consanguinity will account for it; (2) that there are real "cancer houses," the dwellers in which, in the absence of blood relationship, are nevertheless successively or simultaneously attacked by malignant tumors; (3) that cases of malignant disease attacking two persons living together are relatively frequent; and (4) that of one hundred such cases, eighty-five were man and wife, and eight were medical practitioners, who had been engaged in the treatment of cases of malignant disease. According to Guelliot, these facts show that cancer is an infectious disease which is transmitted directly or indirectly by contagion.

Noël (1897) finds that in "cancer districts" certain contagious, tumor-like growths are often seen on the trees, which have a certain resemblance to malignant tumors. He thinks that between these "arboreal cancers" and human malignant disease there is some etiological connection, for the latter are of frequent occurrence in persons living surrounded by or near woods. Cancer of the lip, he says, never originates in Lyons; but all those who present the disease in that city are found to have contracted the disease in the country. Noël considers that Moran has proved that insects, especially large wasps, have a special predilection for "arboreal cancers"; and that they carry the infection not only from tree to tree, but also disseminate it (through orchards, etc.) in human foods. He maintains that human beings may thus be infected when the contagion enters by the mouth, gastro-intestinal lesions resulting, while external parts are attacked through contact infection.

Behla (1898) believes that cancer is a parasitic disease, which may be propagated like malaria; and both maladies have, he thinks, some relation to damp, marshy conditions of soil. He says that differences in the soil, in the well water, or in the atmospheric conditions cannot account for the divèrsities in the incidence of the disease which are noted in different sections of the town of Lockan; thus only the food remains. The inhabitants of the suburb in which cancer is prevalent are mainly small farmers and nurserymen, who eat large quantities of the uncooked vegetables which they raise—cabbages, radishes, lettuces, etc. Behla then points out that these plants are liable to tumor-like diseases of parasitic origin, such as that caused in cabbages by *Plasmodiophora brassicæ*. He has found drinking-water and vegetables teeming with these parasites, which he maintains are the infective agents of human cancer. The great frequency of gastrointestinal cancer points to the food as the means by which the contagion enters the body.

D'Arcy Power (1899) claims to have demonstrated localized epidemics of cancer in certain districts, villages, houses, and "even in a

single room"; but beyond the bold narration of certain exceptional occurrences, which of themselves are by no means convincing, he has not even attempted to prove his thesis.

In 1899 a committee, appointed by the Birmingham branch of the British Medical Association, also investigated the influence of locality on the incidence of malignant tumors, in parts of Warwickshire, Staffordshire, Shropshire, and Worcestershire. They concluded that there were districts in which this disease occurs with a frequency much above the average, side by side with other districts in which it is rare. The high-mortality districts were usually poorly-drained, flat, low-lying, or bordering on streams; whereas the low-mortality districts were high, dry, and well drained. They believe that there is a direct connection between the presence of subsoil water within a certain distance of the surface, and the prevalence of malignant disease.

They also found that second and third cases of cancer occur in particular houses more frequently than can be accounted for by coincidence, that particular groups of houses, perhaps in the same street, might be similarly affected; and they suggest that this association implies contaminated soil. Old houses also appeared to furnish a higher proportion of cancer cases than new ones.

Lloyd Jones (1899) has worked out the local distribution of malignant disease in Cambridge and its vicinity, during a period of nineteen years. He concludes as follows: (1) That some parts of the town are comparatively free from the disease, while other parts, often contiguous, suffer severely; (2) that elevated sites are less liable than low-lying ones; (3) that the chalk subsoil is the freest from the disease; (4) that proximity to the river is not always attended by a high cancer death rate, though damp sites favor the disease; (5) that proximity to trees, especially large ones, in some way favors the prevalence of cancer; (6) that decaying vegetation, filth, collections of manure, etc., are often found in cancer districts.

Mason (1902) has in like manner examined the problem of cancer distribution for the Leamington district of Warwickshire. He believes, whatever the ultimate cause of the disease may be, that it will be found to be associated with a sewage-contaminated subsoil; that end houses of rows, corner houses of streets, and houses on either side of court entries are often "cancer houses," owing to drain leakages and consequent sewage contamination being most frequent at such spots; that old houses are more dangerous than modern ones for the like reason; and that houses built on porous subsoil (sandstone, gravel, etc.) are more prone to favor the development of cancer than those built on clay.

Bosc (1898), having noticed the frequency of parasites and parasitic tumor-like swellings in fishes, believes that many outbreaks

of cancerous disease are due to this cause. He thinks that gastrointestinal cancer is often caused by the bones of small fish wounding parts of the alimentary canal. External cancers, he maintains, are often due to infection carried by insects and various animals; by contaminated fingers and polluted water; and even by fleas, bugs, etc.

Symons has made a careful inquiry as to the relation of cancer to the dwelling-house, as it occurs in Bath, a town which has a high cancer death rate. Much importance attaches to this research, as it is the only instance of the kind in which the subject has been treated in a really scientific manner. Bath has a population of about fifty-two thousand, of whom two-thirds are females, and its population has been stationary for the last half-century. This large excess of females is mainly due to the considerable number of young women employed there as domestic servants, etc.

It contains an unusually high proportion of elderly persons, and comparatively few children under five years of age. Its population comprises a greater number of persons of "independent means" than almost any other town in England. Its general health and sanitary condition are good, typhoid fever and infectious diseases are rare, its general mortality is low, and in all these respects progressive improvement is noticeable; yet withal, its cancer mortality is very high, and for the last half-century it has been steadily increasing, until at the present time its corrected death rate from this cause is fifty per cent. in excess of the average.

This city is situated in a deep valley, which is traversed by a sluggish, sewage-contaminated river, prone to flood the adjacent lands; it has a dense surface soil, overlying lias and oölite, which is permeated by numerous ground springs, the water being very hard. The town is closely surrounded and somewhat shut in by steep, and in some places precipitous hills, from three hundred to five hundred feet high, some of which abut on the town; so that, although most of the houses lie in the hollow, some are built on the slopes of the hills, and most of the best residential houses enjoy quite elevated sites.

In order to get at the facts as to the precise local distribution of malignant disease in the town, Symons located the houses, 1,212 in number, in which 1,319 deaths from this cause had occurred during a period of 32 years (1866–97) among 8,507 houses. Of the houses in which these deaths occurred, the great majority, viz., 1,111, had only a single fatality in each house; in 95 houses there had been 2 fatal cases; and there were 6 houses in which 3 cancer deaths had occurred. These numbers were so little in excess of those that the usual mathematical methods of calculating probabilities indicated that Symons concluded neither the elevation, nor the aspect, nor the class of house

had any constant relation to the incidence of the disease; and thus it was proved, so far as Bath was concerned, that there were no "cancer houses" there.

Applying this method to the data for Cambridge, as compiled by Lloyd Jones, who found that in 19 years there were, among 5,685 houses, 438 houses which were affected with cancer, of which only 7 houses had double cases and 3 triple ones, Symons showed that this proportion of multiple fatalities was actually less than that indicated by the calculated probabilities; so that in Cambridge also there were shown to be no "cancer houses."

From these facts it may be inferred that there is no scientific basis for the doctrine of "cancer houses."

Remarks.—No evidence in support of the infectious or contagious nature of malignant disease is forthcoming from any of the great hospitals in which large numbers of cases of this kind are constantly under treatment. During my eight years' connection with the Middlesex Hospital, although I was daily in the cancer wards, I never noticed a single fact that could possibly be construed in this sense. But I noticed many significant facts, which seemed clearly to indicate that the disease was neither infectious nor contagious. At that time the wards were densely packed with patients in advanced stages of cancer, mostly of the breast and uterus, in a state of ulceration. There were no day rooms for these patients. They lived and died in the same wards. No sooner was one dead than her place was taken by another. The crowding was great. Yet, during a period of twenty years, not a single instance is known in which a nursing sister, probationer, nurse, ward servant, surgeon, student, or any one engaged in attendance on the cancer patients ever acquired the disease. The nursing sister in charge held her office for over a quarter of a century, but she was never affected. Among the cancer patients were several who had inadvertently been admitted with chronic ulcerative affections of a non-cancerous nature. Some of these lived amid the horrors of the cancer wards for many years, but none of them ever took the disease.

Moreover, if cancer were really infectious and contagious, it would surely be, like tuberculosis, of more frequent occurrence in urban than in rural districts; whereas the statistics for this country show just the reverse—in fact, the disease is least frequent of all in those parts of our great towns where the density of population is greatest and where sanitation is least regarded. Hence we never hear of "cancer epidemics" arising in the overcrowded parts of our great cities; but it is rather from remote, sparsely populated, rural districts that all the instances of this kind hitherto reported have come.

In this respect then, as in others, the evidence as to the existence

of a specific cancer microbe has broken down; hence, if there really be any irritant *ab extra*, from whose action malignant disease must result, I can only conclude that it altogether transcends present experience. As a French pathologist has tritely remarked: "Le microbe du cancer, à la vérité, n'est pas encore trouvé; mais on sent que la question est à l'ordre du jour."

TREATMENT OF CANCER.

(INCLUDING SARCOMA.)

BY

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NEW YORK.

WHILE space will not permit an extensive addition to my previous monograph on the "Symptomatology and Treatment of Cancer," I believe it very desirable to record the more recent advances, especially in the direction of new methods of treatment of malignant disease.

Roentgen Rays in Cancer.

A year ago there would have been little need of discussing new methods of treating cancer. Yet such has been the progress in the therapeutic use of the Roentgen ray in cancer during this time that this method, though still in the experimental stage, challenges serious consideration.

This application of the *x*-ray in the treatment of malignant disease seems to have been a gradual evolution; it was first used in lupus with brilliant success, then in cases resembling lupus, but proving to be rodent ulcer.

Until very recently rodent ulcer, or the small superficial epitheliomas of the face and lip, were regarded as the only form of cancer likely to be benefited by the *x*-ray. Just who was the first to try it on the larger and more deeply seated tumors I am unable to say. Malcolm Morris and Sequeira in England and Williams of this country deserve great credit for bringing the attention of the profession to its advantages in epithelioma; and while Williams has been conservative in estimating its value in other forms of cancer, he has steadily enlarged its scope as fast as experience would warrant. Gilman and Pusey of Chicago were among the first to use the method in inoperable carcinoma or malignant disease in general. Gilman states that since July, 1896, he has treated a large number of tuberculous patients and twenty-five cases of true cancer and allied troubles, with a loss of two cases only, one an epithelioma of the throat, the other a scirrhus of the left breast. In June, 1900, Gilman treated a case of advanced

carcinoma of the breast with the *x*-ray and the result was so remarkable that it merits a few details. The bone-like induration extended from below the margin of the ribs to the top of the shoulder. The axillary glands were so much swollen and enlarged as seriously to interfere with the circulation of the arm. In the left axilla were numerous indurated and enlarged glands. The breast itself was a shapeless mass of nodules breaking down in suppurating ulcers; so profuse and offensive was the discharge that it required dressing several times a day. The *x*-ray treatment was begun and continued every other day. Within six weeks the discharge had ceased entirely, the circulation in the arm was restored, and the swollen axillary glands were softer and disappearing. The progress continued, and in January, 1901, there was less than two square inches of diseased tissue.

As far as I have been able to ascertain from a careful search in the literature of the Roentgen rays, this treatment has been employed in but a very small number of cases of sarcoma.

Dr. Williams, in a recent paper read before the New York Academy of Medicine, stated that he had one case of spindle-celled sarcoma which showed marked improvement.

Dr. A. W. Pusey, who has done so much and such excellent work with the *x*-ray in malignant disease, in a recent paper, entitled "Report of Cases Treated with Roentgen Rays," reports four cases of tuberculosis of the skin, eight cases of epithelioma of the face and nose, five cases of carcinoma of the breast, six of deep-seated carcinoma of the neck and head, four of carcinoma of the abdominal cavity, but only three cases of sarcoma. One of these, a case of osteosarcoma of the right shoulder with cachexia and evidence of general sarcomatosis, had six exposures without effect upon the tumor other than giving considerable relief from pain. The second case, that of a woman sixty years of age, with extensive inoperable sarcoma of the right pectoral muscles and shoulder, was treated for a month, with considerable relief from pain, but with no apparent effect upon the tumor. The third case was that of a man, aged twenty-four years, with a history of round-celled sarcoma of the left side of the neck, first noticed in February, 1901. Four months later a tumor developed on the right side. In August, 1901, the primary tumor was removed by Dr. Ochsner, and the patient was sent to Dr. Pusey, on September 2d, for the *x*-ray treatment of the other side. At the time of the beginning of the treatment there was a hard, diffuse swelling, immovable, rendering the neck almost completely rigid. Under one month's *x*-ray exposures this tumor entirely disappeared, as shown by the two photographs in the article. The patient gained twelve pounds in weight. Five months later, however, there was a slight recurrence. Further treatment was advised, but the patient thought it impossible to return to

the city. The diagnosis of this case was made by Dr. F. R. Zeit, associate professor of pathology at the Northwestern University, who stated that it was unquestionably small round-celled sarcoma.*

Under date of November 16th, 1901, Carl Beck, of New York published a case of recurrent melanosarcoma of the thigh and groin in which the *x*-rays showed a very decided inhibitory action. There was marked improvement, but the case was too far advanced to expect a cure. The patient has since died.

The next case, in point of time, that I have been able to find is that of a round-celled sarcoma of the neck, treated by Dr. C. E. Skinner of New Haven, and published by Dr. Frank A. Kirby in the *Journal of Advanced Therapeutics*, February, 1902. This case is a very striking one and deserves to be referred to in detail.

The patient, male, aged 64 years, three years ago received a blow from a wagon pole, leaving a contusion which lasted about a week. Two months later a swelling appeared at the site of the injury. This grew very slowly for about sixteen months, when the patient severely wrenched his neck. Almost immediately afterward the tumor began to grow more rapidly and became painful. By November, 1901, the tumor had become very large and occupied the greater portion of the left mastoid and cervical region, measurements being seven inches laterally, ten inches vertically, with some ulceration and breaking down. Microscopical examination by Dr. Archibald McNeal, of the New Haven Board of Health, showed the tumor to be round-celled sarcoma.

The *x*-ray treatment was begun November 20th, 1901, by Dr. Skinner, a Van Houten & Ten Broeck 32-inch plate static machine being used. Dr. Skinner states that in the incredibly short space of time of six weeks the patient was apparently cured, the tumor having disappeared, the surface healed, and the patient being free from pain and able to resume his work.

On June 27th, 1902, I made a personal examination of this case and found the following:

In the left side of the neck and mastoid region is a very large, broad cicatrix, measuring two and one-half by three and one-half inches, but there is absolutely no trace of a recurrent growth. In the lower part of the cervical region there can be felt, on deep pressure, very slight enlargement of one or two of the deep cervical glands, apparently not larger than peas.

Inasmuch as so few cases of sarcoma have as yet been treated by the *x*-ray, I feel justified in giving a brief sketch of the histories of my own cases. The whole method is still in the experimental stage, and I do not pretend that the technique that I have employed should

* In the discussion of the paper (June 5th, 1902) Dr. Ochsner stated that the patient had returned to Chicago for treatment, and that the recurrent growth had again disappeared under the *x*-ray.

be taken as a guide for others. I merely wish to place these cases before you as a slight addition to the slender data we now possess upon which to base an opinion as to the therapeutic value of the Roentgen ray upon malignant tumors.

CASE I.—*Inoperable Round-Celled Lymphosarcoma of Neck, Pectoral Region, and Axilla.*—M. L. A——, a lady 40 years of age, first noticed a tumor just above the clavicle, about two years ago. This was removed. Shortly after this a recurrence was noted in the right cervical region, which grew with great rapidity, very quickly involving the axillary glands on the same side. In July, 1900, the axillary tumor was removed by Dr. C. B. Nancrede, of Ann Arbor, Mich. The tumor in the cervical region showed such extensive involvement of the deeper structures that it was considered entirely inoperable. Microscopical examination was made by Dr. King, of the Dartmouth Medical School, who pronounced it small round-celled sarcoma. The patient was referred to me by Dr. Nancrede for the toxin treatment, in October, 1900. Physical examination at this time showed a large tumor in the right cervical region, extending from the clavicle to the mastoid process of the temporal bone. There were some enlarged nodules below the clavicle and several small tumors in the region of the cicatrix in the axilla. The toxins were begun at the General Memorial Hospital, October 1st, 1900, and continued with intervals of rest for six months. There was a very decided decrease in the size of the tumors and increase in their mobility. This continued for about three months, and then in spite of further injections the improvement ceased. At the end of six months the growth slowly began to increase in size and it was not thought wise further to continue the injections. Since June, 1901, no treatment further than palliative has been used, and the patient has since then been awaiting with great courage and composure what was regarded as the inevitable and not long-to-be-delayed end. The tumors slowly but steadily increased in size, and in the beginning of March, 1902, her condition was as follows: A tumor mass encircled the entire neck, ending at the vertebral line and extending from the mastoid process to the clavicle on the left side, on the right side involving the entire cervical, supraclavicular, pectoral, and axillary region, about the size of two fists. The largest protuberance was in the right cervical region. The constriction of the trachea was so great as to cause frequent and severe attacks of dyspnœa. She was confined to the bed the greater part of the time. Without hope of causing even temporary improvement, but more as a matter of experiment I determined to try the *x*-ray. The treatment was begun February 10th, 1902, four to five exposures per week, at a distance of eight inches, being given. At the end of three weeks a marvellous change had taken place. The tumor masses had decreased fully one-third in size and had become very movable. A small burn was produced in the upper right cervical region over the most protuberant part of the tumor. The skin in this place had become very thin from the pressure of the tumor. The burn healed in about two weeks. The treatment was kept up at the rate of four exposures a week until June 15th, at which time the tumors, both in the neck and axilla, had entirely disappeared. On June 8th the only remaining nodule, just beneath the

right sternomastoid muscle and about the size of a marble (one-half inch in diameter), was removed as a matter of pathological interest. It was examined by Dr. George P. Biggs, pathologist to the New York Hospital, and his report showed the typical appearance of round-celled sarcoma with some degenerative changes.

The patient has entirely regained her health and left the hospital July 8th, 1902, to go to the country.

October 9th, 1902. The patient now shows a small recurrence in the right upper cervical region, with glandular enlargement in both groins evidently of metastatic origin. The treatment has been resumed.

CASE II.—*Sarcoma of the Femur.*—A. G——, aged 19 years, first noticed a swelling in the lower portion of the left femur in November, 1901. This gradually increased in size and was accompanied by loss of weight and deterioration of general health. The patient came under my observation February 5th, 1902. At that time physical examination showed a large tumor, extending from the condyles of the left femur to the junction of the middle and upper thirds. The tumor consisted of a fusiform enlargement of the entire lower two-thirds of the femur; on the outer aspect of the thigh, about one and one-half inches above the joint, there was a soft, fluctuating area, just covered by thin and reddened skin. There was slight impairment of the functions of the joint, but no swelling of the joint itself. An incision was made under cocaine into the fluctuating area and three ounces of clear serum, similar to that which is found in cystic degeneration of sarcomatous tissue, was evacuated. The curette passed into the cavity of the bone, and typical sarcomatous tissue was removed. Microscopical examination by Dr. E. K. Dunham showed it to be round-celled sarcoma. The patient absolutely refused operation, although he was told this was the only thing that offered any hope of saving his life. The *x*-ray treatment was tried entirely as an experiment, with the result that the tumor decreased one inch in circumference. After a month's treatment the exposures were discontinued for two weeks, at the end of which time the tumor had increased nearly an inch in size. The treatment was again resumed and the growth slowly decreased in size, until at the end of another month the circumference of the thigh over the centre of the tumor was one inch less than the original measurement. The treatment has been continued four times a week up to the present time, June 3d, with slow decrease in the size of the tumor, although the patient has lost two pounds in weight. During the last week, however, he has developed signs in the right lung which point very strongly toward beginning of metastases. The tumor shows a decrease of two inches from the original measurements.

October 9th, 1902.—The patient has gained twenty pounds in weight, and the femur has returned to nearly its normal size.

CASE III.—*Small Round-Celled Sarcoma of the Pectoral Region.*—E. M——, aged 35 years. Family history good. First noticed a tumor in the right pectoral region, near the anterior axillary line, in the latter part of 1898. This grew rapidly in size and was operated upon by Dr. Maurice H. Richardson, in November, 1900. The tumor at

that time was the size of a fist. Extensive removal of the mass and part of the muscle was made. Microscopical examination by Dr. W. F. Whitney, pathologist to the Massachusetts General Hospital, showed the growth to be small round-celled sarcoma. The tumor recurred a few months after operation and grew very rapidly. A second operation was performed in October, 1901. The disease then involved the pectoral and axillary region so widely that it was found impossible to remove it. Amputation of the upper extremity was considered, but not thought advisable. The patient was referred to me by Dr. Maurice H. Richardson, in December, 1901, for the mixed toxin treatment. The toxins, prepared by Dr. B. H. Buxton, were administered five to six times a week for a period of three months, the doses being gradually increased until a reaction of 102°–103° was produced. The tumor began to soften and spontaneous opening occurred in January, 1902, with evacuation of about a pint of necrosed tumor tissue. The growth had thus considerably diminished in size, when on February 10th, 1902, I began *x*-ray treatment which was continue for two weeks, without any further decrease in the size of the tumor. The toxins and *x*-ray were then given in combination, four times a week, and since this time the growth has steadily and rapidly decreased in size. One week ago the patient was able to clasp his hands behind the back, for the first time in eight months. The mass in the axilla has entirely disappeared, movements of the shoulder, which were greatly restricted, are practically normal, and there now remains only a very small, freely movable mass, not more than two inches in diameter and very superficial, in the pectoral region. This was believed to be only the induration caused by the toxin injections, and a specimen removed under cocaine, June 7th, proved, on microscopical examination by Dr. E. K. Dunham, the pathologist of the General Memorial Hospital, this supposition to be correct, and no evidence of malignancy could be found. The patient has remained in good health, and was discharged, apparently well, June 8th, 1902.

(Later note.) Physical examination, made June 27th, 1902, shows the small area of induration mentioned before, and proven by the microscope to be non-malignant, to have entirely disappeared. The patient is in the best of health.

As an indication of the hopelessness of this case, I will quote from a letter received from Dr. Richardson, under date of May 6th, 1902:

"I feel so sure that he is going to die that I have told him not to accept any discount on the face of his life insurance policy. In other words, I have not the least confidence in his ultimate cure."

CASE IV.—*Round-Celled Sarcoma of the Fascia of the Thigh.*—M. V——, female, aged 37 years, was referred to me in March, 1900, by Dr. Charles Peck, of New York. At the time of her admission to the General Memorial Hospital there was a tumor at the site of the recent cicatrix in the anterior and upper portion of the left thigh. She had had two operations at the French Hospital during the past six months, the last one, a very extensive operation, having been done six weeks before. The tumor, when I first saw her, was about three inches in

diameter. Both the toxins and *x*-rays were tried for a month, neither having the slightest apparent effect in decreasing the size of the tumor, which was of rapid growth. The treatment was then abandoned.

CASE V.—*Small Round-Celled Recurrent Sarcoma of the Back.*—Disappearance under two months' treatment with *x*-rays. W. J——, 8 years. Family history good. In the latter part of August, 1901, the patient fell from the stoop, striking the back. Two to three weeks later the mother noticed a swelling over the left scapular region, which increased in size rather rapidly. It was soft and fluctuating from the beginning. The patient was referred to me in December, 1901, by Dr. Polhemus, of Nyack, New York.

Physical examination at that time showed a cystic swelling, the size of an orange, in the left scapular region. The skin was normal, the tumor fluctuating, situated apparently just beneath the skin and superficial fascia. The diagnosis of hæmatoma was made, and on the 12th of January an incision was made under ether anæsthesia and several ounces of dark blood were withdrawn with a small trocar. There was no evidence of any tumor at this time. The wound was closed without drainage and healed by primary union. Two to three weeks later, the tumor slowly began to reform; it was still cystic in character and increased steadily in size, until on May 6th it had become about one-third larger than prior to the first operation. A second operation was performed. This time, in addition to fluid blood and clots, there was a slight thickening of the walls of the cyst, which made me suspect sarcoma. A portion of this thickened tissue was removed and examined by Dr. H. T. Brooks, professor of pathology to the Post-Graduate Hospital, who pronounced it small round-celled sarcoma.

Two weeks after the operation, before the wound had entirely healed, the *x*-ray treatment was begun and continued three times a week until July 30th, 1902. At present (October 9th, 1902) the tumor has entirely disappeared and the boy is in perfect health.

In addition to these cases I have watched with great interest four patients with inoperable sarcoma who had been for a long time under my observation, and on whom the toxins of erysipelas had been carefully tried, but without success.

CASE VI.—*Small Round-Celled Sarcoma of the Neck, Six Times Recurrent.*—G. F. H——, 70 years of age. About thirteen years ago a lump was first noticed in the left side of the neck. Nine years ago this was removed at the New York Hospital. The tumor recurred one year later in the scar and grew much larger. The patient has had four subsequent operations within the last seven years. One tumor was removed from the right side of the neck, the others recurring in the region of the cicatrix of the original growth on the left side and behind the ear. The pathological records of the New York Hospital show the following:

"G. F. H——, aged 60 years, has had a tumor on the left side of the neck, posterior to the scalenus anticus muscle for three years and four months. Of slow growth at first, the tumor has increased in size

rapidly during the last three months. No glands were involved. Operation February 20th, 1892. The specimen is an oval tumor seven by four and one-half inches; no capsule; on surface the voluntary muscle fibres are seen invaded by the tumor tissue at several points. Microscopically the tumor is a typical round-celled sarcoma with small amount of fibrous tissue stroma, apparently derived from tissues in which the growth originated."

On May 13th, 1901, the patient was referred to me by Dr. E. M. Foote, of the Vanderbilt Clinic, as a case of inoperable sarcoma of the neck for the treatment with the erysipelas toxins. Physical examination at that time showed a tumor, the size of an orange, occupying the left mastoid region. The tumor was very vascular and semifluctuating. There was glandular involvement behind the jaw on the right side; also a growth, the size of a small orange, in the right femoral region. There was a hard, freely movable, glandular tumor in the right axilla, the size of an English walnut. The patient was treated with the mixed toxins of erysipelas and bacillus prodigiosus from May 13th to June 5th, during which time thirteen injections were given, the highest temperature reached being 102° F. On June 5th I tied the external carotid artery on the left side, under ether anæsthesia, using chromicized tendon for the ligature. The wound healed by primary union and the patient then left the hospital, but returned July 16th for another course of the toxin treatment and remained until July 27th —eleven days. At first there was some slight improvement following the injections of the mixed toxins, but later on there seemed to be very little, if any, influence from the treatment. The patient seemed to become rather tired of hospital life and was discouraged. He returned home on the 27th of July, the tumor at that time being about the same size as when he entered the hospital, the base occupying the mastoid region and extending down to the neck, pushing the ear forward. It was not attached to the bone, but was absolutely inoperable, and, as I believed, hopeless.

December 22d, 1901, Dr. E. R. Fiske, of Brooklyn, started the *x*-ray treatment. The patient states that he had been trying for several years to find a physician or surgeon to give him the *x*-ray treatment, but failed until Dr. Fiske took him in charge, offering to give him two weeks' trial, but holding out very little hope as to the result. A static machine was used and exposures of ten minutes' duration each day were made for two weeks when the treatment was continued for a further two weeks, the exposures being made for fifteen minutes. At the end of four weeks' time the exposures were lengthened to twenty minutes. In all the patient had six weeks' treatment. His condition at the time of the beginning of the treatment was as follows: On the left side of the neck, just behind the ear and extending downward, was a large tumor, fully the size of two fists, pushing the ear far forward. There was also in the right axillary region a tumor the size of a goose egg. Almost immediate improvement was noticed after the beginning of the treatment and the mass rapidly diminished in size; at the end of four weeks it had entirely disappeared. The patient states that after three or four weeks of *x*-ray treatment he noticed a softening of the tumor in the right axilla, although no exposures were made in any other region except the neck. This softening continued and the tumor gradually disappeared until February 20th, 1902, it could scarcely be

felt. At the *x*-ray meeting of the Academy of Medicine, March 9th, 1902, I showed the patient in perfect health, and there was not the slightest suspicion of tumor or induration in the neck. The tumor in the right axilla had also disappeared.

(Later note.) On June 19th, 1902, I made a careful examination of the patient and there is no trace of a recurrence. Since April, 1902, he has had *x*-ray treatment for nodules in both groins (size of an egg), and they have disappeared from the left, and nearly disappeared from the right groin.

This case is certainly one of the most remarkable of its kind yet recorded, showing the beneficial influence of the *x*-rays upon sarcoma. The repeated recurrences, together with the numerous microscopical examinations at the New York Hospital, place the diagnosis absolutely beyond a doubt.

CASE VII.—*Spindle-Celled Sarcoma of the Abdominal Wall.*—M. J. H——, female, aged 34 years, was referred to me by Dr. Maurice H. Richardson, of Boston, on April 19th, 1901. The patient had a well-marked family history of malignant disease. She had been operated upon three years before for what was regarded as a fibroid tumor of the uterus; tubes and ovaries also were removed. No microscopical examination was made. Two months ago she first noticed a hard tumor in the lower part of the abdominal wall in the region of the cicatrix. There was no pain, no discomfort, but rapid increase in size. When the patient came under my care, physical examination showed a tumor, the size of a cocoanut, in the lower part of the abdomen, filling up the entire iliac fossa, extending nearly to the umbilicus and two inches beyond the median line to the left. The tumor was very firmly fixed and seemed to involve the abdominal wall. An incision was made under cocaine and a portion of the growth, which infiltrated all the muscles of the abdominal wall, was removed for microscopical examination, which showed it to be fibrosarcoma. The erysipelas toxins were used for ten months. During the first two months the growth decreased more than half in size, and for a long time thereafter, while there was no decrease, there was no distinct growth. Later on, the influence of the toxins seemed to have become lost, and there was a slow but gradual increase in size. In January, 1902, the tumor was growing rapidly, and at this time the abdomen had the appearance of that of a woman seven months pregnant. I advised a trial with the *x*-rays and the patient went to New Haven, Conn., where she has since been under the care of Dr. Clarence Skinner and has had regular, systematic treatment. She had *x*-ray treatment two to three times a week from January to June, 1902. At first there was decided improvement in general health, and some slight decrease in the size of the tumor. When I last saw her in May, 1902, the tumor appeared larger, and since then her health has been failing, and there is little doubt that the disease is beyond control.

CASE VII.—*Recurrent Small Round-Celled Sarcoma of the Superior Maxilla.*—W. D. L——, aged 38 years, a dentist, was operated upon

by Dr. William T. Bull in the spring of 1901 for small round-celled sarcoma of the superior maxilla, with excision of the entire bone with exception of the orbital plate. The growth promptly recurred and three secondary operations were performed by Dr. Bull and myself, the last one in August, 1901. The patient was treated with the mixed toxins of erysipelas and bacillus prodigiosus for several months by Dr. Gertrude Kelly, under my direction, with temporary improvement and some decrease in the size of the tumor. But at length the toxins seemed to have no further effect, and an attempt was made to procure erysipelas by inoculating living erysipelas cultures. A slight attack was produced with much improvement in the condition of the growth. Soon, however, the tumor began to grow rapidly and involved a large portion of the cheek and nose, causing exophthalmus of the left eye. Feeling sure that nothing further could be done by either operation or the toxins, I referred the patient to Dr. W. B. Snow in the latter part of January, 1902, for the *x*-ray treatment. Dr. Snow has treated him three to four times a week ever since, with a static machine, and the growth has not only been checked, but has diminished very markedly since.

Examination, July 17th, 1902, showed the patient's condition by far the best that it had been any time since the *x*-ray treatment was begun. A great deal of the deeper portion of the tumor had sloughed out through the mouth. The exophthalmos had nearly disappeared, and the nose, which had been greatly deformed and enlarged by the growth, was nearly normal.

October 9th, 1902.—The patient's condition has been growing worse during the past month. The disease has evidently been extending into the sinuses, and there is no hope of a permanent cure.

CASE VIII.—*Recurrent Osteosarcoma of Side of Head, Mastoid Region, and Parotid.*—S. M——, female, aged 22 years, four years ago first noticed a tumor just in front of the right ear. This was excised, but was followed by a recurrence a year later. The recurrent growth was treated with caustics, without success. The patient was referred to me for the toxin treatment by Dr. Kinnaird, of Lexington, Ky., in October, 1900. Physical examination at that time showed a tumor involving the mastoid region of the temporal bone, completely surrounding the ear and forming a mass, the size of an English walnut, in the parotid region. The growth originated in the bone, was absolutely fixed; the skin over the parotid portion was normal and not adherent. The posterior tumor projected to the level of the ear and the skin was involved and destroyed, being replaced by a series of hard, small, round, reddish protuberances, with little tendency to ulceration. The tumor was unquestionably a sarcoma, although no microscopical examination was made. The patient suffered agonizing pain, for which large doses of morphine were required. She had lost much flesh and strength and her pulse ranged between 100 and 120. The toxins were given for three months, but her condition was so poor that she was never able to receive more than from one-fifth to one-third of a drop injected into the tumor. Even these small doses produced some decrease in the size of the growth and slight improvement in her general condition. At the end of three months she returned home and the

treatment was continued for three months by her family physician. After the treatment was discontinued the tumor slowly began to increase in size, and she returned to New York for further treatment in November, 1900. The tumor had increased considerably in size, the mass behind the ear being the size of a hen's egg and the mass in front nearly as large, although the skin was normal. It presented the appearance of a uniform, cone-like bulging of the entire side of the head, the external auditory meatus of the ear occupying the apex of the cone. The tumor was extremely sensitive to the touch and the pain was more severe than the year before, requiring one-half grain of morphine every two hours to give her moderate relief. She was still much emaciated, pulse was weak and rapid (110–120 per minute). Her susceptibility to the toxins was still marked; a dose of not more than one-fourth of a minim would produce a severe chill and temperature of 102°–103° and marked prostration. She was treated with minute doses (one-fifth drop) four times a week, for three months, up to the middle of January. While there was apparently no increase in growth, there was no decided decrease, and inasmuch as it was impossible to give her larger doses, I believed it useless to continue the treatment. Having carefully followed the results obtained by the *x*-ray treatment in epithelioma and a few cases of carcinomatous nodules in the breast, I thought it worth while to try the effects of the *x*-ray treatment before abandoning the case as hopeless, and accordingly referred the patient to Dr. William J. Morton on the 25th of January, 1902. Since then she has been treated four times a week by Dr. Morton, with ten to twelve minutes' exposures, at a distance of from eight to ten inches. The immediate effect of the treatment was a marked influence upon the pain, which ceased almost entirely after three to four treatments, and there has been very little pain since, making it possible for her nearly to discontinue her morphine. The effect upon the tumor was an immediate decrease in size and a marked diminution of pain. The exposures were continued three times a week until the first of June, nearly five months. At the end of this time the tumor had so nearly disappeared that there was no longer any protuberance and the outline of the two sides of the head practically the same. Her general condition, however, did not improve, and during the last weeks of May she lost flesh and strength. The first week in June there was an acute cellulitis of the right cervical region with high temperature and severe pain. A thick, very foul-smelling discharge appeared at the same time from the right ear. After a few days I opened the cervical swelling under a local anæsthetic and evacuated a large amount of pus. The discharge from the wound, and ears as well, soon decreased under careful irrigation and ceased entirely in two weeks. The patient's condition was very critical at this time, but she slowly improved in general condition.

Whether the tumor has been completely destroyed it is at present difficult to state.

While none of these cases can as yet be reported as a cure, they nevertheless furnish the strongest ground for encouragement. It seems proved that in a certain proportion of malignant tumors we have found an agent that will cause the disappearance of the growth

after all other means have failed. Whether the patients will remain well sufficiently long to justify us in calling them cured, time alone will tell. The entire disappearance of a large tumor of the neck in four patients—Skinner's (of New Haven), Pusey's (of Chicago), Fiske's (of Brooklyn), and my own, the diagnosis of sarcoma being confirmed in every case by competent pathologists, give us great cause for congratulation. When we consider how large a proportion of sarcomas have their origin in the neck, and how hopeless they have proved to operative treatment, we realize the importance of these recent observations.

My experience with the *x*-ray treatment of carcinoma is limited to twenty-four cases observed in private practice, and at the General Memorial Hospital. Twelve of these cases were of recurrent carcinoma of the breast, in two of which small nodules disappeared after a few weeks' treatment, but soon returned. The epitheliomas of the face showed great improvement; the deep-seated growths of uterus, bladder, and rectum showed very little benefit as regarded either the size of the growth or the intensity of the pain.

From a study of these cases of carcinoma I believe that the action of the *x*-ray upon carcinoma is slightly less marked than in sarcoma.

In my collection of two hundred and seven personal cases of sarcoma analyzed in Vol. XVII. of this work, no less than sixteen cases were primary in the neck. I have never yet seen a case of sarcoma of the neck cured by operation, nor have I been able to find an authentic case reported by other surgeons; hence, if in the *x*-ray we have a means of destroying these growths, or a certain proportion of them, it means a great advance over present methods.

As regards the action of the *x*-ray, no one has as yet been able to explain just how the *x*-ray influences malignant tumors. There have been a great many opinions advanced, but none is susceptible of proof. Pusey states that "his sections show that the *x*-rays cause a degeneration of some sort of carcinomatous tissue and a disappearance of this degenerated substance, presumably by absorption. However it occurs, the fact remains that gross embryonic tissues and other tissues of low vitality are made to disappear under the influence of *x*-rays, without destruction of the uninvaded healthy tissue, and such a fact is pregnant with possibilities."

Personally I believe that there are strong reasons for regarding the action of the *x*-rays upon malignant tumors as new evidence in favor of the microparasitic origin of such tumors. In support of this view I would cite the fact that nearly all lesions in which the *x*-ray has been used with such beneficial effect are of known or probable microbic origin, *e.g.*, lupus, tuberculous disease of various forms, and many varieties of skin disease, including alopecia areata. Further

evidence pointing to the infectious nature of malignant tumor, especially sarcoma, is found in the recent successful transplantation of sarcoma in animals of the same species by Loeb. It will be objected by some that the *x*-rays are not bactericidal or to only a slight degree. The answer would be that the action of the *x*-ray in a test-tube culture of a given germ might be of a very different kind from the action of the same rays in the living body, with the possibility of forming some chemical change in the living tissues that might destroy the organisms or inhibit their growth.

It is worthy of note that in the two cases in which the tumors (both large inoperable round-celled sarcomas) have almost completely disappeared, the patients had been treated with the mixed toxins of erysipelas and bacillus prodigiosus for several months. In one case the tumor had diminished at least two-thirds in size as a result of the toxins and then showed little improvement from the *x*-ray alone; and in the other, while the growth was not checked entirely, the toxin treatment had a marked inhibitory action as evidenced by the slower progress of the disease.

Proper Limits of the x-Ray Treatment.

The question will naturally arise, In what class of cases should the treatment be employed? We must confess that the method is still in the experimental stage; and while in this stage, I do not believe it wise to employ it except in inoperable cases or in cases in which serious deformity would result from the operation—*e.g.*, facial cancer or cancer involving the eyelid or nose. There is, however, a possibility that, if the present results prove permanent, it will supersede operative treatment in very many cases, especially cases in which operation would necessitate the amputation of a limb.

Conclusions.—I am conscious that the present series of cases is too small and the time of observation too short to justify one in drawing any dogmatic conclusions as to the permanent therapeutic value of the Roentgen ray in sarcoma. Still, I believe, we are warranted in stating:

1. That the results in the cases thus far treated prove that the Roentgen ray has a remarkable inhibitory action upon the growth of all forms of malignant disease, and that this is especially true of sarcoma.

2. That this action in many cases of even far advanced and inoperable malignant disease may result in the total disappearance of the tumors, often without any breaking down of the tissues, the new growth being apparently absorbed.

3. Whether the patients have been cured, or the disease has been merely arrested to reappear at some future date, is a question that time alone can decide.

4. Recent observations and experiments upon the various forms of carcinoma and sarcoma prove that an agent, supposed to be of value only in a very limited class of superficial epitheliomas, promises to be of as great or greater value in practically every variety of cancer.

5. While at present there is little evidence to show that deep-seated tumors in the abdomen and pelvis can be cured or benefited by the Roentgen ray, there is still some reason to hope that with improved apparatus or with greater knowledge and skill in using the apparatus that we now have, even these cases may be benefited.

6. The Roentgen ray has a very marked influence upon the pain of nearly all types of malignant tumors, causing entire relief in the majority of cases.

Treatment with Mixed Toxins.

Since the publication of my former article in this work, sufficient time has elapsed to make it possible to give a truer estimate of the value of the mixed toxins of erysipelas and bacillus prodigiosus in the treatment of inoperable sarcoma.

At the meeting of the American Surgical Association, at Baltimore, in 1902, I gave a history of the final results of the cases that have been successfully treated by this method. I referred to a paper published by me in 1898, covering my results in 140 cases of inoperable sarcoma treated with the mixed toxins. In 24 of these the tumor completely or partly disappeared. Eighty-four of this series were round-celled sarcoma; 21 spindle-celled; 9 melanotic sarcoma; 2 chondrosarcoma; 12 were sarcoma (diagnosis confirmed by the microscope, but type of cell not stated); 6 were inoperable sarcoma resting on clinical diagnosis combined with a history of repeated recurrence in most cases.

In 40, or slightly less than half of the round-celled cases, there was more or less improvement, as shown by decrease in size and cessation of growth. In only 3 of these was the treatment successful.

Of the 21 cases of spindle-celled sarcoma, 10 disappeared entirely, and all the remainder showed marked improvement.

In melanotic sarcoma, as I have stated, I have had no successes. It should be noted, however, that Dr. George R. Fowler, of Brooklyn, has reported one case of melanotic sarcoma of the tonsil and fauces, which entirely disappeared under the use of the mixed toxins. The patient remained well for two years, when a local recurrence followed and proved fatal.

In addition to these personal results, the paper contained a summary of results in 35 cases successfully treated by other surgeons employing the same method. Of these 35 cases, 10 were round-celled, 10 spindle-celled; in 5 the diagnosis was clinical only; in 5 there was,

in addition to the clinical signs of sarcoma, a history of recurrence after operation; in 4 the diagnosis of sarcoma was confirmed by microscopical examination, but the type not stated; 1 was an endotheliosarcoma.

Of these 35 cases, 26 disappeared completely; 2 others decreased so much that only a small node was left, which was easily excised. One of the latter cases was well three years, and the other one year at the time of the report.

Of the 35 cases referred to, 14 were well over two years, and 6 cases over three years.

While at the time of my report in 1898, 8 of my own cases had remained well from three to six years, I was able, in my paper of last May, to report 16 cases that had remained well from three to eight and one-half years. Of these 2 recurred after three and eight years respectively, 1 dying of metastases in the abdomen; the second, after remaining well for eight years, died of local recurrence.

The cases were all hopeless, inoperable cases, and the diagnosis was confirmed by the microscope with two exceptions. In these instances the history of the cases, with the clinical appearances, made the diagnosis of sarcoma unquestionable. The type of tumor in the 15 cases that passed the three-year limit was as follows: Spindle-celled sarcoma, 9; round-celled sarcoma, 2; mixed-celled sarcoma, 2; epithelioma, 1; sarcoma (clinical diagnosis only), 2.

It is worthy of special note that two of the successful cases, now well three and three-quarter and four and one-quarter years respectively, were sarcoma of the parotid gland. Butlin, in his last edition of "Operative Treatment of Malignant Tumors," states that: "Up to the present time there are very few instances of cure by operation of undoubtedly malignant disease of the parotid." In my two cases treated by the toxins, the diagnosis was not only confirmed by a competent pathologist, but, further, by a history of repeated recurrences after operation. Another case still is also worthy of special mention, inasmuch as it shows that the toxins may be taken for long periods of time without harm. The patient, a well-known physician, with eight times recurrent spindle-celled sarcoma of the soft parts of the chest (anteriorly) was treated with small doses of the mixed toxins with varying intervals of rest, for upward of two years. The patient regained his usual health, and has now been perfectly well over six years from the beginning and four years since the cessation of the treatment. The tumors, while originally pure spindle-celled, were becoming more mixed with round cells and more vascular with each recurrence; in other words, the disease, as so often happens, was increasing in malignancy until the toxins were begun.

In addition to these sixteen cases that have passed the three-year

limit, in eight others the tumors disappeared. One, a spindle-celled sarcoma of the abdominal wall, was well one and one-half years, when the patient returned to her home in Europe and was lost sight of. Another, an extensive round-celled sarcoma of the iliac fossa, was well one year and then lost sight of. A third, a spindle-celled, recurrent sarcoma of the leg, is now in perfect health, without recurrence, two and three-quarters years after treatment. A fourth, a twice recurrent, spindle-celled sarcoma of the palm of the hand, disappeared, and the patient remained well two and a half years, when the tumor recurred. Refusing amputation of the arm, she was under the care of a Christian scientist for eight months, during which time the tumor in the hand reached the size of a cocoanut and extended above the elbow. I then amputated the arm just below the shoulder-joint, but she died of metastases three and one-half months later.

A fifth case, a chondrosarcoma of the ilium, of large size, disappeared, and the patient, after remaining well for seven months, had a recurrence, which proved fatal in about a year's time. A sixth, a round-celled angiosarcoma of the breast, was well six months later, when the patient was lost sight of. A seventh, a recurrent fibroangioma of the lip, was well when last heard of, over two years after operation; and an eighth, a recurrent, spindle-celled sarcoma of the thigh, disappeared, but the patient, after remaining well for a year, had a recurrence locally and in the groin, which no longer yielded to the treatment.

In addition to these twenty-four personal cases, I would mention two other cases in which I directed the treatment, although it was carried out by another surgeon. One case (Johnson's), a large, spindle-celled sarcoma of the pharynx, entirely disappeared, and the patient was well more than six years later. The second (Storr's and Griswold's) inoperable sarcoma of the breast and axilla, disappeared under seventy-eight injections of the mixed toxins, and is now well more than four years after treatment. The diagnosis in both of these cases was confirmed by microscopical examination, in the latter case by one of the highest authorities in this country, Prof. William H. Welch, of Johns Hopkins University.

During the past year there have been several additional successes, even more striking than any of the earlier cases. One of these, an inoperable round-celled sarcoma of the upper jaw with metastases, the diagnosis of which was confirmed by Prof. William H. Welch, of Johns Hopkins University, was fully reported in the *Medical Record*, May 3d, 1902. This case, treated under my direction by Dr. O. K. Winberg, of Lake Park, Minn., was in so desperate a condition that I hardly think I should have advised the treatment had I been consulted before the injections were begun. The treatment was employed in

large doses for a period of six months, one hundred and three injections in all being given. The patient was presented by me before the surgical section of the New York Academy of Medicine. No trace of the tumor was left; abdominal examination showed nothing abnormal. On October 1st, 1902, the patient was still in good health.

Another remarkable case was that of a patient with round-celled sarcoma of the parotid, the diagnosis having been confirmed by Prof. William H. Welch, of the Johns Hopkins University. This case was absolutely inoperable and given up as hopeless; yet the tumor entirely disappeared after eight months of continuous treatment with small doses of the toxins. The patient has remained, up to the present time, in perfect health, two years after the beginning of the treatment.

Results of Operation for Cancer of the Breast.

First a few words in regard to the methods of operation. I still hold to the opinion that the present statistics do not justify the introduction of the elaborate operation of removing the supraclavicular glands, advocated by Halsted, as a routine measure. In many cases it may be desirable to remove the pectoral muscle alone with the fascia, as by this means easier access is obtained to the axillary space, and removal of the glands is facilitated.

When the supraclavicular glands have become involved, I believe that the life of the patient can seldom, if ever, be saved by the most extensive operation. Far more important than removal of the supraclavicular glands is an extensive and far-reaching removal of the skin, as statistics of recurrences show that the chances of a return in the skin are about fifteen to one to recurrence in the pectoral muscle or supraclavicular glands.

While results from the more extensive operations up to date have shown great improvement over those of a few years ago, I still believe that there is a tendency at present to give a better prognosis than is warranted by the facts. I have long maintained that the three-year limit furnishes by no means a satisfactory estimate as to the number of cures. This view was strongly supported by the very complete statistics of Sir W. Mitchell Banks, who, in a series of two hundred and fifty personal cases traced for long periods of time, showed that twenty-six per cent. of the cases that remained well for three years subsequently showed a return. Instead of a percentage of fifty or sixty of permanent cures after operation, reported by some surgeons who still make use of the three-year limit, I believe twenty-five per cent. to be much nearer the truth if the patients are traced to final results.

In my former article the method of treating inoperable mammary cancer by removal of the ovaries (Beatson's operation) was described

and commented upon adversely. Since that time many more cases have been operated upon by surgeons in different countries, and it is possible to give a more accurate estimate as to the value of this operation. In my former paper I ventured the explanation that the marked improvement that undoubtedly did follow the removal of the ovaries in a certain number of cases was due to diminished vascularity of the mammary region that resulted from the operation. This explanation has recently received the support of no less an authority than A. Marmaduke Sheild. His opinion of this method is as follows:

"As regards the true value of the operation of removal of the ovaries after recurrent mammary cancer, I fear I must say that I regard this proceeding as quite experimental. That a certain number of cases have been benefited, I have no doubt; that a number have received no benefit whatever, I am equally certain. My own personal experience is limited to two cases; they were both bad types of recurrent cancer in young vascular women. In neither of these did the slightest benefit occur. I also know of three private cases in which the operation was performed by other surgeons, and no benefit was obtained. I believe that the true reason why improvement—the withering of cancerous nodules, the relief from pain, and so on—has followed removal of the ovaries in certain cases, is due to diminished vascularity of the mammary region, sometimes caused by the operation. In certain cases of removal of the ovaries the breasts atrophy, hair grows on the lip, the patient generally emaciates, and mental conditions of the women become altered and curious. This change, it is well known, is by no means universal or even common, but should it occur, the diminution of vascular supply to the mammary region would certainly markedly arrest the development of mammary cancer."

Mr. Boyd, in 1900, collected fifty-four cases in which oöphorectomy had been performed for cancer of the breast. These were by no means selected cases, but included the whole experience of several surgeons. It is Mr. Boyd's opinion that the operation probably prolonged life, on an average, for six months. Out of the fifty-four cases, nineteen, or thirty-five per cent., were more or less markedly benefited by the operation, one died. Boyd believes that oöphorectomy should be proposed in all cases, except the very acute, of inoperable cancer of the breast, in women over forty years with no visceral or bony lesions, and before the menopause. Cancer in other parts of the body, even the uterus, is not affected by oöphorectomy.

Personally I have never believed the chances of permanent improvement sufficiently great to warrant advising the operation, and certainly, at present, in view of the remarkable improvement derived from the *x*-ray treatment in inoperable cancer of the breast, without operation, there is no longer any reason for considering the operation in question.

TUBERCULOSIS.

BY

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IT was my privilege to contribute to the TWENTIETH CENTURY PRACTICE OF MEDICINE, Vol. XX., that portion of the article on tuberculosis which refers to diagnosis, prognosis, prophylaxis, and treatment. Since the publication of the volume two years have elapsed. In the following pages we shall discuss the changes which have been accepted, and the definite progress that has been made, and add whatever is new concerning the social aspect of pulmonary tuberculosis since the appearance of the chapter on that subject two years ago.

Diagnosis.

Before I speak of what is really new I must refer once more to something but relatively new, which was discussed freely in Vol. XX., namely, the use of tuberculin as a means of demonstrating the presence of incipient pulmonary tuberculosis. I have not changed my views in regard to the employment of tuberculin, as either a diagnostic or a therapeutical agent. I am as strongly opposed to it to-day as I ever was; but during the past year statistics have been published at various times claiming to show the absolute harmlessness of the tuberculin injection. The tuberculin test, however, still proves to be not always reliable. In some patients who suffered from pulmonary consumption beyond a shadow of doubt no tuberculin reaction could be obtained. On the other hand, anæmic, chlorotic, cancerous, syphilitic, and actinomycotic patients reacted. It has been said that in obscure cases of lung filtration, other than tuberculous, the tuberculin test is the only means of making a differential diagnosis. The recent painstaking investigations of Naegeli, of Zurich, demonstrate that ninety-six per cent. of adults who had died of other than tuberculous diseases showed latent tuberculous foci somewhere in their bodies. In view of the great frequency of tuberculosis in other organs besides the lungs, for example in the glands and bones, as demonstrated by this and other investigators, a differential diagnosis from syphilis, acti-

nomycosis, carcinoma, sarcoma, or echinococcus of the lungs is by no means assured by the injection of tuberculin.

Serious accidents which manifest themselves in human beings after a trial injection of tuberculin are rare, but not rare enough to warrant the routine use of tuberculin for a diagnostic purpose in the human race. One of the saddest accidents of this kind came to my notice recently. A veterinarian, seemingly in the best of health, inoculated himself accidentally with a small quantity of tuberculin while testing cattle for tuberculosis. Typical reaction followed and within three months the man died from tuberculosis. This veterinary surgeon probably had a latent tuberculosis, but it seems to me reasonable to suppose that he would have lived a good many years like any number of others who go around with latent tuberculosis, had his dormant lesions not been awakened by the inflammatory activity caused by the tuberculin.

The advocates of the tuberculin test in the human race say: "Be careful to use small doses and no harm can happen." As an answer to this I may be permitted to quote from a recent lecture on "Early Recognition of Tuberculosis," delivered last year before the physicians of Frankfort-on-the-Main by Dr. Carl Hess, the chief of the Falkenstein Sanatorium and the successor to Dettweiler. Depreciating its use in general he says: "Ich habe bei selbst vorsichtiger Anwendung kleiner Tuberkulin Dosen ernste Schädigungen gesehen." (I have seen serious damage even by the careful use of small doses of tuberculin.) Dr. Hess stands to-day as one of the best and most experienced clinicians in this particular branch of medicine.

In a recent discussion on the use of tuberculin, Professor Janeway of this city recalled the case of a young man suffering from early tuberculosis, in which, according to his belief, a generalization of the tuberculous process resulted from a trial injection of tuberculin made by the family physician. Prof. E. A. de Schweinitz, in an article on "The Present Status of the Use of Tuberculin and the Products Obtained Directly or Indirectly from the Tubercle Bacilli in Tuberculosis," concludes with the following words: "In general, conservative experimenters are of the opinion that tuberculin should be used most carefully for diagnostic purposes because certain toxic products of the bacilli might cause deleterious results."

If in presence of an individual with subjective symptoms of early tuberculosis, the physical signs of which even the greatest care in examination fails to reveal, I institute the hygienic and dietetic treatment, and if possible send my patient away on a vacation. I have then the absolute assurance of having done no harm, but may perhaps have saved a human life by timely treatment at the onset of an obscure tuberculous trouble.

Our modern means of physical diagnosis with the aid of an intelligent anamnesis and the *x*-rays should, however, suffice to clear up nearly all doubtful cases in which bacteriological evidence cannot be obtained. During the past few years *x*-ray work has received a great stimulus, and the number of physicians who resort to this valuable adjuvant has increased, and thus also our knowledge on the subject has grown. It has been exceedingly gratifying to me to see so high an authority as Dr. Francis H. Williams, of Boston, who in former years used tuberculin extensively, make the following statement: "I find the use of tuberculin less and less necessary as my experience with *x*-ray examinations, used in connection with other methods of examination, increases. I say 'in connection with other methods of examination' advisedly. For example, we may find slight and doubtful signs in one lung by auscultation and percussion, suggestive of tuberculosis, and if the *x*-rays give evidence confirmatory of this disease, there is plainly less need for the use of the tuberculin test than there would otherwise have been, or it may not be required at all." In his book, "The Roentgen Rays in Medicine and Surgery" (The Macmillan Company, 1901), Williams speaks of the use of the *x*-rays as follows: "By *x*-ray examinations we detect abnormal conditions of the lungs, their change in density, elasticity, and volume; and to some extent they assist us to make a differential diagnosis, as will be seen later; but the shaded apex and shortened excursion of the diaphragm seen in pulmonary tuberculosis may also point to a recent pneumonia in the upper lobe, and the history of the case would be necessary to enable us to discriminate between this cause and tuberculosis; or again, the movement of the lung might be restricted by a pneumonia with pleurisy which had caused adhesions. Therefore the inquiry should be made as to whether or not the patient had previously had pneumonia or pleurisy. But the darkened apex and shortened excursion of the diaphragm should always make the physician consider pulmonary tuberculosis, and put him on his guard against a beginning of an old and healed tuberculosis. The history of the case, however, and further examinations, are necessary to make a positive diagnosis."

The classes of cases of pulmonary tuberculosis, in which, according to Williams, the *x*-ray examination is of value, are:

"A. As an aid in diagnosis. (1) In cases where there are no physical signs, or where they are very doubtful; (2) in cases where there are slight physical signs only; (3) in cases where an accompanying emphysema, bronchitis, pleurisy, or pneumonia may disguise the physical signs of tuberculosis; (4) in cases where the physical signs indicate tuberculosis, which the *x*-rays do not confirm; (5) in cases of tuberculosis of some other portion of the body than the lungs, to see if they are also affected; (6) in patients between fifteen and thirty

years of age where the family history is tuberculous. Precautionary *x*-ray examinations.

"B. In old lesions of tuberculosis.

"C. For determining existing conditions more accurately.

"D. In determining the progress and extent of disease. (1) in cases where the progress of the disease is rapid, *x*-ray examinations made at intervals of a week or so will often show marked increase in the diseased area, although to physical signs the progress is not so evident; (2) in cases where the progress is not rapid and the patients gain steadily in weight and improve in color and general condition, and have no temperature, yet the *x*-rays show that the disease is steadily advancing.

"E. In determining the extent of disease. In cases in which the *x*-rays assist us to determine the extent of the disease as well as its progress, and enable the physician to determine whether the patient should or should not remain at home.

"F. In acute miliary tuberculosis.

"G. In showing cavities in the lungs."

In my own experience in *x*-ray work, which is not so long nor so great as that of Dr. Williams, I have had occasion to see this author's conclusions verified. I have confined myself in my examinations to the simple use of the fluoroscope. I have never met with an accident arising from its use, since a long exposure to the rays is not necessary. I have had patients faint shortly after being placed before the Crookes tube, owing to the excitement, to the novelty, or to fear. I have since learned to prepare timid patients for the procedure by showing them on my assistant or on their hands the workings of the *x*-rays.

Whether the examination of the patient should be made in the recumbent or the standing position largely depends upon the choice of the examining physician. To make a careful diagram of the Roentgen picture of the lung with mathematical precision, a table for that purpose is indispensable. Whether making an *x*-ray examination with the fluoroscope or screen, or taking an *x*-ray photograph, it is important that both the patient and the physician should be comfortable during the examination. If measurements are taken it is, of course, essential that the position of the patient during the subsequent examinations shall always be the same, and in this case Williams' elevated canvas table is indispensable. For recording the appearance seen on the fluorescent screen, Williams' method of tracing made on a thin sheet of glass or film of celluloid can be done without removal of clothing. If the clothing is removed the tracings can be made upon the skin.

The work on the agglutination test for diagnosing an early tuberculosis does not seem to have made any marked progress since the

appearance of the twentieth volume of this work. At the recent Tuberculosis Congress in London, Arloing, Courmont, and Buard again brought forth their claims for the agglutination test in pulmonary tuberculosis as a valuable means in the early diagnosis. Koch, who has recently experimented with serum agglutination with a view to apply the test as a standard to estimate the actual progress accomplished by immunization by repeated subcutaneous injections of small amounts of tubercle bacilli dust, tested thirty persons without, and seventy-eight persons with, tuberculosis. He found that the agglutinating reaction occurred spontaneously in a number of subjects in each group, thus showing incidentally that it has no value for early diagnosis of the disease. To our experience and experiments, set forth in connection with this subject in the article in the twentieth volume, we have therefore nothing to add, and say again that further investigation is necessary before the serum diagnosis in pulmonary tuberculosis can be considered a reliable means.

Prognosis.

In prognosis, however, the agglutination test might be considered of indisputed value, since nearly all experimenters have noticed that, if there is a reaction, the degree of the agglutination varies in the inverse ratio of the disease, that is to say, the more advanced the case the less marked is the agglutination; the earlier the case the more pronounced the agglutinating power of the serum.

The diazo reaction is still looked upon as a fairly reliable means of making a prognosis. But as I have stated in former writings, I should prefer to suspend judgment in a seemingly favorable case, though a positive diazo reaction had been obtained. I am rather inclined now to seek help in making a prognosis in the fluoroscopic picture obtained with the help of the x-rays. The larger the field of transparent pulmonary tissue the brighter may be our hopes for the patient's future, taking, of course, into consideration all the other well-known factors of a favorable prognosis, such as a fairly good heart, little or no dyspnœa, a good digestion, the means to carry out the dietetic treatment, a cheerful and hopeful disposition, absolute obedience, favorable hygienic environments, and the possibility of constant medical supervision.

Prophylaxis.

In the field of prophylaxis much has been done during the past two years. We will first speak of bovine tuberculosis in its relation to human tuberculosis, which has received so much attention since Koch's address at the London Congress, entitled "The Combating of Tuber-

culosis in the Light of the Experience that has been Gained in the Successful Combating of Other Infectious Diseases." In this address he said that experiments had been made which led him to conclude that tuberculosis was not transmitted from the lower animals to man. Tuberculosis had been observed in almost all domestic animals, most frequently in poultry and cattle. The tuberculosis of poultry differed so much from human tuberculosis that it might be left out of account as a source of infection. Bovine tuberculosis remained to be considered. During two years, in conjunction with Professor Schütz, of the Veterinary College in Berlin, he had carried out a series of experiments. A number of young cattle which had stood the tuberculin test, and might therefore be regarded as free from tuberculosis, were infected in various ways with pure cultures of tubercle bacilli taken from human subjects of tuberculosis; some directly with the tuberculous sputum of consumptive patients. In some cases the tubercle bacilli or the sputum were injected under the skin, in others into the jugular vein. Six animals were fed with tuberculous sputum almost daily for seven or eight months; four repeatedly inhaled great quantities of bacilli, which were distributed in water, and scattered with it in the form of spray. None showed any symptoms of disease, and they gained considerably in weight. From six to eight months after the beginning of the experiments they were killed. In their internal organs not a trace of tuberculosis was found. Only at the places where the injections had been made small suppurative foci had been formed in which a few tubercle bacilli could be found. This is exactly what occurs when dead tubercle bacilli are injected under the skin of animals liable to contagion. They were affected by the living bacilli of human tuberculosis exactly as they would have been by dead ones; they were absolutely insusceptible to them. The result was different, however, when the same experiment was made on cattle free from tuberculosis with tubercle bacilli from the lungs of an animal suffering from bovine tuberculosis. After an inoculation period of about a week the severest tuberculous disorders of the intestinal organs broke out in all the infected animals and some died of the disease in a month and a half.

An almost equally striking distinction between human and bovine tuberculosis was shown by a feeding experiment with swine. Six young swine were fed daily for three months with the tuberculous sputum of consumptive patients. Six other swine received the bacilli of bovine tuberculosis with their food daily for the same period. The animals fed with sputum remained healthy; those fed with the bovine bacilli soon became sickly, and half of them died. After three months and a half the survivors were killed and examined. In those fed with sputum no trace of tuberculosis was found, except here and there little

nodules in the lymphatic glands of the neck, and in one case a few gray granules in the lungs. The animals, on the other hand, fed on the bovine bacilli all showed severe lesions, especially tuberculous infiltration of the greatly enlarged cervical lymphatic glands, the mesenteric glands, and extensive tuberculosis of the lungs and spleen. The difference between human and bovine tuberculosis was not less striking in similar experiments on asses, sheep, and goats. Thus, human tuberculosis differed from bovine, and could not be transmitted to cattle.

But what of the far more important question of the susceptibility of man to bovine tuberculosis? A direct answer was not possible, because experimental investigation was out of the question. However, there were certain facts bearing on it. Milk and butter often contained large quantities of the living bacilli of bovine tuberculosis, which numbers of persons daily consumed without becoming infected. It was thought that tuberculosis could be conveyed by aliment, but primary tuberculosis of the intestine was extremely rare. In a large number of necropsies in cases of tuberculosis, Koch had seen primary intestinal tuberculosis only twice. At the Charité Hospital, in Berlin, ten cases of primary tuberculosis of the intestine occurred in five years. In 933 cases of tuberculosis in children, Baginsky never found tuberculosis of the intestine without simultaneous disease of the lungs and bronchial glands. In 3,104 necropsies in tuberculous children, Biedert observed only 16 cases of primary tuberculosis of the intestine. Such cases were as probably due to the widely propagated bacilli of human tuberculosis as to those of bovine tuberculosis. Hitherto it could not be decided with certainty whether tuberculosis of the intestine was of human or of animal origin. Now they could be diagnosed. All that is necessary is to cultivate the bacilli and inoculate cattle with them by subcutaneous injection. Koch estimated that the extent of infection by milk and flesh of tuberculous cattle was hardly greater than that from hereditary transmission, and therefore he did not think that precautions against it were advisable.

To those of us who listened to this address the revelations came as a surprise, and the subsequent discussion revealed that the views of few of the men present coincided with those of Koch. It will be of historical interest to cite here a few of the extemporaneous replies to Koch's statement that bovine tuberculosis was incommunicable to man. Lord Lister said that even if the human disease could not infect cattle, the converse did not follow, and it would be of the most serious consequence should they relax their efforts to secure a safe milk supply and then the view put forward prove erroneous. The great variety of intestinal infection was the main argument, but mesenteric tuberculosis existed and was not rare in children. Professor Nocard, of the Alfort

Veterinarian School in France, repudiated the conclusions as to the non-communicability of the bovine disease. He held that experimental researches in France proved tuberculosis to be transmissible from man to cattle and *vice versa*. Professor Bang, of Copenhagen, said he could not accept Dr. Koch's conclusion, and feared the opinion of so great an authority might prove detrimental by causing a relaxation in the efforts now being made in all directions to secure the purity of milk. Professor Sims Woodhead, of Cambridge, was convinced that bovine tuberculosis had played a considerable part in the extension of the disease among mankind.

Since the publication of Koch's address numerous experiments to prove or disprove his assertions have been carried on in the United States and in other countries, and incidentally the fact has been revealed that similar work to that done by Koch and his German collaborator had been previously done by Theobald Smith in the United States, by Adami in Canada, and by others. In justice to these workers it seems but right to quote here from Professor Adami's recent work, "On the Relationship between Human and Bovine Tuberculosis," wherein he refers to the experimental work which antedated Koch's, as follows: "As I have pointed out elsewhere (*Canadian Journal of Medicine and Surgery*, November, 1901), and as others in the United States have noted, Koch by no means gives to American workers the credit that is their due. In 1893 Gaiser, working under Baumgarten, of Tübingen, had inoculated one cow with human, another with bovine bacilli, and had obtained negative results with the former and rapidly developing miliary tuberculosis with the latter. This, it will be seen, was a single observation, and it attracted little attention. The credit lies with Frothingham, Theobald Smith, and Dinwiddie, who, by carefully planned experiments free from all sources of error, established the fact that cattle are in general immune to pure cultures of tubercle bacilli derived from man. Koch and Schütz at most confirmed these observations, which, it may be added, appeared before these last observers began their series of studies."

Professor Adami's conclusions represent, we believe, to-day the consensus of opinions of all who have studied the subject without prejudice, and thus we take pleasure in reproducing them here:

"1. Bovine tuberculosis is easily conveyed from cattle to cattle and, whether by inhalation (the most common method), by the milk (in calves), by contamination of stalls and drinking-water through the agency of the saliva and nasal discharge, through the genitourinary passages, or by intrauterine infection (very rare), this transmission from one animal of the bovine species to another is far and away the commonest mode of infection in cattle, so common that for practical purposes all other modes may be neglected.

"2. Human tuberculosis is transmissible to cattle. Pure cultures of these bacilli rarely cause infection. Mixtures of tubercle bacilli with other microrganisms (as in sputum) appear to be more infectious. The difficulty in introducing artificial tuberculosis favors the idea that natural infection of cattle with human tubercle bacilli must be of singularly rare occurrence.

"3. Swine appear to be fairly easily infected with both human and bovine tubercle bacilli; and when infected with the former these gain an increased virulence for guinea-pigs and rabbits. But while through the use of infected milk these animals become frequently infected from cattle, conditions favoring the reverse process are rare. Thus, while it may occasionally be that swine, or possibly other domestic animals, act as intermediaries in the passage of tuberculosis from human beings to cattle, the conditions favoring such transmission from man to the hog, or from the hog to cattle, so rarely show themselves that again, for practical purposes, this mode of infection may be neglected.

"4. If this be so, it should be possible to eradicate bovine tuberculosis in a region in which human tuberculosis continues to be widespread.

"5. Human tuberculosis in the majority of cases is conveyed from human being to human being by inhalation, more rarely it is conveyed through the alimentary tract, still more rarely through the genital tract, through surface wounds, and from the mother to the fœtus during intrauterine life.

"6. Everything points to the fact that in the main the bacilli causing infection in man are derived from previous cases of the disease in man.

"7. By sojourn in the human body and passage from man to man the human tubercle bacilli have acquired properties differing from those acquired by bacilli which have passed through cattle: their shape differs, the rate of growth and the appearance of the growths outside the body are different; their virulence toward the animals of the laboratory is also different.

"8. These differences are not, however, sufficiently marked or constant enough to permit us to conclude that we are dealing with distinct species. On the contrary, the evidence at our disposal points clearly to the fact that in the different species of animals we encounter at most *races* of tubercle bacilli, which by growth in the bodies of animals of another species take on the characteristics of the race of bacilli peculiar to that species.

"9. Bovine tuberculosis can be transmitted to man, and this either through wounds or through the digestive tract.

"10. By passage through cattle the tubercle bacillus gains increased

virulence for cattle, rabbits, and guinea-pigs, but lessened virulence for man and (it would seem also) for carnivorous animals.

"11. Save in the very rare cases of wound infection, there is a significant lack of evidence that bovine tubercle bacilli infect adult human beings.

"12. It is infants and those of early age who are liable to be infected by the tubercle bacilli of bovine origin, and this through the agency of milk. The statistics bearing upon the continued frequency of tuberculosis in children and upon the relative frequency of intestinal and abdominal tuberculosis in children must be accepted as conclusive evidence upon this point.

"13. Even with children a consideration of the great frequency of bovine tuberculosis in certain regions and of the absence of any record of tuberculosis affecting those supplied from a given "milk round," leads to the conclusion that the bovine bacilli have not heightened virulence.

"14. The few positive records we possess of direct transmission of tuberculosis from cattle to man through the agency of the milk indicate that infection is brought about only by the employment of milk of cattle which are very extensively diseased, more especially of those suffering from udder disease. Such milk contains enormous numbers of bacilli. In other words, large numbers of tubercle bacilli are required in order to infect human beings with bovine tuberculosis. This again is an indication that the bacillus cannot be regarded as having gained a heightened virulence for man, and that infection is not very readily communicated.

"15. Animals showing physical signs of tuberculosis (for mild grades of the disease afford no physical signs), and, above all, those exhibiting udder tuberculosis, should therefore be condemned and under no condition should their milk be used for food.

"16. Where there is tuberculosis in a herd, Bang's method should be employed, the animals reacting to tuberculin being separated from the healthy ones; the milk from the reacting animals for whatever purpose used, should be pasteurized so as effectively to destroy the tubercle bacilli.

"17. The great cause of infantile mortality is inflammation of the stomach and intestines (gastroenteritis and diarrhœa), and this is proved to be mainly brought about by the use of badly kept and fermenting milk. Wholly apart, therefore, from the question of tuberculosis it is imperatively necessary that greater care should be exercised by all concerned in the distribution of milk, the general measures taken to lessen this, the greatest scourge of childhood (prohibition of use of milk from cattle showing *any* form of sickness, pasteurization of milk, etc.), will equally lessen the danger of the transmission of tuberculosis from cattle to man."

Ravenell, who has made bovine tuberculosis in its relation to the human race a life study, concludes his remarkable work on "The Intercommunicability of Human and Bovine Tuberculosis" as follows: "The evidence at hand forces us to conclude that human and bovine tuberculosis are but slightly different manifestations of one and the same disease, and that they are intercommunicable. Bovine tuberculosis is, therefore, a menace to human health. We are not in a position at present to define positively the extent of the danger, but that it really exists cannot be denied. In the past there has probably been a tendency to exaggeration; but however great this may have been, it does not now justify any attempt at belittling the risk, and it is folly to blind ourselves to it. The eradication of bovine tuberculosis is amply justifiable from a purely economical standpoint; viewed in its bearing on human health it becomes a public duty."

I should like to add here what I stated publicly at the conclusion of the congress in London concerning bovine tuberculosis, namely, that I should urge the continuance of all precautions which have been hitherto inaugurated concerning the prevention of the spread of tuberculosis from beast to man, from man to beast, or from beast to beast.

The ingestion of any tuberculous product cannot be healthful even if the result should not be an exact reproduction of the morphological conditions which were characteristic of the pathogenic microorganisms ingested. Again, all bacteriologists agree that bacilli, cocci, etc., of a given species, when transplanted into an organism which is not their usual habitat, may nevertheless adapt themselves and acquire the characteristic of the type usually peculiar to that organism. What we think the precautions should be to stop the spread of bovine tuberculosis of whatever source are described in full in the section on "The Prevention of Tuberculosis in Cattle and Other Domestic Animals," in Vol. XX. of this work.

Treatment.

Concerning the strictly medicinal treatment of tuberculosis in its pulmonary or laryngeal form, there have as usual been put before the profession a great many remedies with more or less pronounced claims for specific action. Our personal experience with some of them and the perusal of the literature on the results obtained with others have convinced us that we are as yet as far away as ever from a specific medicinal agent in the combating of tuberculous diseases. We will mention some of the more important of these new remedies, which we are willing to class as adjuvants.

First we desire to speak of the administration of *urea* as a new remedy. There is no doubt that a gouty diathesis is antagonistic to

tuberculosis. Many physicians have noticed this fact. Dr. Henry Harper, of Nottingham, England, has had perhaps more experience than any one else in the administration of urea in consumption. He goes so far as to assert that urea exerts a specific action in tuberculosis, quite as marked as mercury in syphilis. While we would not be willing to share Dr. Harper's enthusiasm, we are willing to concede to urea a favorable action in some cases of tuberculosis. In one of his more recent communications Dr. Harper considers only the following cases suitable for the administration of urea: (1) Circumscribed pulmonary tuberculosis of the lung, in which the sputum exhibits abundance of bacilli and only a limited number of cocci; (2) enlarged tuberculous glands situated in any part of the body; (3) tuberculous pleurisy; (4) tuberculous laryngitis; (5) lupus; (6) tuberculosis of the peritoneum with fluid in the peritoneal cavity; (7) hydrocephalus in children; and (8) tabes mesenterica. Cases which are unsuitable are: (1) Pulmonary tuberculosis in which cocci predominate; (2) acute miliary tuberculosis with a high temperature (103° F., or over); (3) gastritis; (4) the last stage of tuberculosis when the patient is dying; and (5) when the patient has a temperature over 101° F.

Mode of administration is to begin with small doses of ten to fifteen grains thrice daily, gradually increasing up to forty, fifty, or sixty grains as a maximum. The best and most obviously apparent good results have been gained from the use of urea in diseases like lupus and superficial tuberculous glands.

The intravenous injection or the administration per os of *sodium cacodylate* is the next most talked-of new antituberculosis remedy. Anelli reports favorable results in advanced cases from daily intravenous injections of 5 cgm. of sodium cacodylate dissolved in 1 c.c. of sterilized water.

Nascent iodine is another of the new antiphthisical remedies recommended. The injection of an iodide into the blood of animals causes the generation of nascent iodine in the lungs, when the animals are afterward forced to inhale the fumes of essential oil of turpentine. After thorough experimental confirmation of this fact, Cavazzini applied it to the treatment of pulmonary tuberculosis in the clinic, and now reports numerous complete cures from this nascent iodine method of treatment during ten years of experience. This simple and effective treatment seems to have no inconveniences except that it requires months and sometimes a year or so before the cure is complete. Some of his patients, Cavazzini says, have remained completely cured for more than six years. He mentions that at first the symptoms become aggravated under this treatment. He applies it in both acute and chronic cases, and claims to have cured patients whose tuberculosis had existed for several years.

Zomotherapy in phthisis, which originated with Richet and Héricourt, has received a new impetus from various investigators. We ourselves have administered raw beef as a most valuable food in the dietetic treatment of pulmonary tuberculosis for a number of years, and we are gratified to see the great interest taken of late in this phase of tuberculotherapeutics. Robinson published recently a very interesting summary of the treatment of phthisis by raw meat as based on the experiments of Richet and Héricourt; the latter consider that "raw meat or the plasma pressed from raw meat acts by the antitoxic agents therein contained, elements which effectively combat the tuberculous intoxication." These experimenters have not yet been able to decide whether the muscle plasma is an antitoxin, whether it stimulates phagocytosis, or whether it is solely a special tonic to the nervous system. The author suggests, in explanation of the action of the plasma, that the nerve cell fixes the ptomains, leucomains, albumins, enzymes, and diastases of the muscle as they circulate in the blood. But the cell saturated with nutritive principles can no longer fix the tuberculin, and thus the evolution of the tuberculous disease can take place without danger to the individual; "the nerve cell has become refractory to the poison."

We may mention finally a new method of applying *electricity* in the treatment of pulmonary tuberculosis. It was set forth by Chisholm Williams, of London, in a paper before the British Medical Association on August 2d, 1901, in which he described his results in the treatment of pulmonary tuberculosis by means of electrical currents of high frequency and high potential. He referred to forty-three cases so treated, all being of a severe type. At first, after each application, the temperature rose, but each successive rise was less, and when no rise followed, arrest of the disease had occurred. Cough was lessened. Expectoration at first was increased, and sometimes became rusty, but its offensiveness lessened, and eventually became almost absent. The number of the bacilli first increased, then decreased. Flesh was put on, and all the symptoms were coincidentally alleviated. The average duration of treatment was about three months. We had recently occasion to witness this treatment applied at the hospital of McGill University, in Montreal. The electrician in charge exhibited a table which showed a general increase in weight of patients submitted to the treatment. The installation of such an apparatus as indicated by Williams, and the time consumed for the treatment, would make the application almost impossible outside of an institution.

In the *symptomatic treatment* of tuberculosis we have only a few new remedies to record. One of the more recent is gelatin as a hæmostatic in pulmonary hemorrhages. Although it has been advised by numerous authors, we think its use is justified only in extreme cases, for

there is always danger from its subcutaneous injection, and it does not seem to be superior in severe cases of hæmoptysis to any of the other styptic remedies. Kühn recently reported a case of fatal tetanus as a consequence of an injection of only 50 gm. of a two-per-cent. solution of gelatin which was made into the inner side of the left leg in order to stop an uncontrollable hemorrhage. The child had been operated upon for adenoids. Whenever the severity of a case justifies the employment of this remedy, the greatest care should be exercised in the selection of the gelatin. The presence of the calcium salts in gelatin seems to be the main factor in hastening coagulation of the blood when given subcutaneously.

A still later remedy in pulmonary hemorrhages is the suprarenal extract, first used and described by W. H. Bates, of New York. It has since been employed in pulmonary hemorrhages in a number of cases with most gratifying results. The best method of administration is perhaps the freshly powdered and well-preserved extract in three to five-grain doses. Floersheim, in an article on "The Use of Suprarenal Extract in Diseases of Heart and Lungs," publishes a number of cases in which the suprarenal extract proved very successful in pulmonary hemorrhages. I myself have not had universally good results, but have had fairly good success in a number of obstinate and chronic cases of hæmoptysis which did not yield to older remedies. The suprarenal extract has of course no effect on the tuberculous process, and its value lies only in the temporary styptic quality and the tonic effect on the heart.

In severe and prolonged hemorrhages Murphy's compression of the bleeding lung may be resorted to. This compression is accomplished by the careful intrapleural injection of nitrogen gas into the affected side. At a meeting of the American Climatological Association in 1901, Loomis reported some cases of hæmoptysis treated by this method, and stated that he had never failed to control the hemorrhage absolutely.

When after the cessation of an excessive pulmonary hemorrhage the patient's condition becomes alarming on account of great loss of blood, subcutaneous injections of decinormal salt solutions have been of value to me in some recent cases. These injections may likewise be resorted to in grave cases of mixed infection to overcome the toxic effects resulting from the secretions of the various microorganisms. Such saline solutions seem to be of particular value when the mixed infection cannot be ameliorated or overcome by antistreptococcic serum. Menthol has become of late a great favorite in the symptomatic treatment, and we can warmly recommend it as an addition to the armamentarium in phthisiotherapy. It is a non-toxic anæsthetic and calms the irritation of the air passages as well as morphine does. A few crystals of menthol are placed on a spoon and heated over a lamp or stove for

from five to twenty seconds. In this way a sufficient amount of menthol vapor is produced for the patient to inhale. A solution of menthol in alcohol, in the strength of from forty to fifty per cent., may also be used, from ten to twenty drops being placed in the hollow of the hand and thus inhaled. In order to dislodge the secretion which lines the bronchi and sometimes interferes with the action of menthol, intratracheal injections of mentholated oil may be given, thus evoking a cough which serves to remove the mucus. Ten to twenty drops of the following liquid, which was recommended in the original article for marked bronchorrhœa, seems well suited for that purpose:

℞ Guaiacol,	
Menthol, ...	ää ♏ x.
Olive oil, ...	ʒi.

The use of lactic acid seems to have been of late much less in favor in the treatment of laryngeal tuberculosis than it was in former years. The majority of laryngologists prefer now orthoform in place of it. A very excellent preparation of orthoform has been suggested by Freudenthal:

℞ Menthol, ...	1, 5, 10 or 15
Ol. amygdal. dulc., ...	80
Vitelli, ...	25
Orthoformi, ...	12.5
Aquæ dest., ...	q.s. ad 100
Ft. emulsio.	

The application is made with the aid of an ordinary laryngeal syringe. For the induction of preliminary local anæsthesia saccharated suprarenal extract is used in place of cocaine.

The Social Aspect of Tuberculosis.

At no epoch in the history of phthisiology have greater strides been made in the combating of tuberculosis as a social disease than during the past two years. The Congress for the Combating of Tuberculosis, which convened at Berlin in 1899, resulted in the formation of a permanent international bureau for the prevention of tuberculosis, with its seat in Berlin. The objects of this bureau are: (1) to collect all news relating to the combating of tuberculosis from various countries; (2) to collect the literature on the subject; (3) to reply to questions relating to the antituberculosis movement; (4) to petition the proper authorities to further the cause; (5) to receive and make suggestions relative to the international combating of tuberculosis, especially as regards investigations, the publication of popular essays, and arranging lectures and meetings; (6) to publish a periodical to be sent free

of charge to all members, containing the reports of the work done by the International Central Commission and discussing other subjects of interest to the cause.

Every country is represented by at least two members, and countries with more than ten million inhabitants are entitled to one more representative for every five million people; but the total number of members for a single country must not exceed five.

What a good example the German subcommittee of this bureau ("Deutsches Central-Komité zur Errichtung von Heilstätten für Lungenkranke") has set may be learned from their recent report. According to it about one hundred sanatoria for the consumptive poor and those of moderate means, accommodating from four thousand to five thousand patients, are at this time in operation throughout Germany. A popular prize essay with the title, "Tuberculosis as a Disease of the Masses and How to Combat It," has been distributed, or sold at cost price, by this committee with the aid of the German Government throughout the empire, the fourth edition of one hundred thousand copies having just been issued. Although this essay is the literary property of the Congress which offered the prize, translations into other languages were generously permitted, and as a result it has appeared in English,* French, Dutch, Spanish, Italian, Portuguese, Russian, Polish, Bulgarian, Roumanian, Hungarian, and Hebrew. Over a million copies of the so-called "Tuberkulose Merkblatt," a little leaflet giving condensed instructions for the prevention of tuberculosis, issued by the Reichs-Gesundheitsamt, have also been distributed.

The next important tuberculosis congress was held in 1900, at Naples. A number of interesting papers were read; nothing new, however, was brought forth.

The memorable British Congress on Tuberculosis, in July, 1901, has been already referred to. Nearly all the civilized nations of the globe were officially represented. Besides the address by Prof. Robert Koch on bovine tuberculosis the most remarkable addresses delivered were on "The Measures Adopted by Different Nations for the Prevention of Consumption," by Professor Brouardel, "Tubercle Bacilli in Cow's Milk as a Source of Tuberculosis in Man," by Professor McFadden, "Sanatoria for Consumptives," by Prof. Clifford Allbutt.

Since the close of this congress England has distinguished itself

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*The American edition, translated by the author, is published by M. Firestack, 110 West 96th Street, New York. The English edition is translated by Dr. J. M. Barbour, and published by Rebman Limited, 129 Shaftesbury Avenue, London. Each edition has, like the original German, a chapter on the social aspect of tuberculosis with reference to the special social conditions prevailing in the country in which it is published.

by a marked activity in the antituberculosis crusade. It has a most prosperous "National Association for the Prevention of Consumption and Other Forms of Tuberculosis," with the King as patron, and the Prince of Wales as president. There are thirty-four vice-presidents, among whom are many of the nobility, prominent medical men, and the presidents of all the royal colleges of physicians and surgeons of the British empire. The Association numbered at the end of 1901 thirteen branches.

In France, where the Government has taken a most active part in the antituberculosis work, there convened in 1902 a congress under the name of "Premier Congrès des Œuvres Antituberculeuses," resulting from a federation of all the French tuberculosis movements. This federation is under the patronage of the President of the Republic, the President of the Senate, the President of the Chamber of Deputies, and the President of the Ministerial Council. Of the importance of such a federation in antituberculosis work we cannot speak too strongly. Nearly all the departments of France were represented, showing a great variety of movements, all tending toward one purpose, namely, the eradication of the disease. Here are the names of a few of the organizations belonging to the federation: "Popular Sanatorium Work," "French League Against Tuberculosis," "Agricultural Colony for Poor Convalescent Consumptives," "Maritime Sanatorium Association," "Maritime Sanatorium for Scrofulous Children," "Society for the Prevention of Tuberculosis and the Gratuitous Placement of Poor Consumptives in Sanatoria," "Work for Tuberculous Children," "Society of Antituberculosis Dispensaries for the Environments of Paris," "Antituberculosis League l'Espoir" (Hope), and the "Dispensary de la rue Turbigo."

Japan, Russia, Austria, Italy, Portugal, Spain, Holland, Denmark, Sweden, and Norway have done similar work, though not on such an extensive scale. In some of the Latin American republics there has also been an awakening, and to judge from the *Revista de la Tuberculosis*, the organ of Liga Argentina contra la Tuberculosis, they are doing excellent work in the Argentine Republic, Chili, Brazil, Uruguay, Paraguay, Bolivia, Ecuador, Peru, Mexico, etc. In January, 1901, in Santiago de Chili there was formed a permanent international commission for the prevention of tuberculosis in Latin America ("Comision Internacional Permanente por la Profilaxia de la Tuberculosis en la America Latina").

In Cuba antituberculosis work is now most active. It was initiated by the United States sanitary authorities, under the direction of Major W. C. Gorgas, chief medical officer of Havana, aided by Surgeon-Major C. L. Furbush and by the antituberculosis society of Cuba, under the presidency of Dr. Emilio Martinez. A sanatorium to be

divided in sections for curable and incurable cases is in course of erection near the city of Havana.

In Canada a vigorous antituberculosis crusade was inaugurated a year ago. The Canadian Association for the Prevention of Consumption and Other Forms of Tuberculosis is most prosperous and is accomplishing a great deal of good by educating the people and furthering the propaganda for the erection of sanatoria. Besides this society there exists in Canada a National Sanatorium Association, incorporated by special act of the Dominion Parliament in 1896. Its object is "to establish a public institution or institutions for the isolation, treatment, and cure of persons affected with pulmonary disease."

In the United States there exists as yet no national association for the prevention of tuberculosis. Up to the time of the writing of this article I could, upon careful inquiry, ascertain that there existed State societies only in Pennsylvania, Colorado, Ohio, Maine, Minnesota, and Illinois. Good work is also done by the following smaller, but active, local societies, viz., The Laennec Society for the Study and Prevention of Tuberculosis" in Baltimore; a similar one in St. Louis, composed of the alumni of the City Hospital; a Cleveland City, a Buffalo, and a Suncook (N. H.) Association for the Prevention of Tuberculosis.

In the city of New York a Committee for the Prevention of Tuberculosis has been recently formed under the auspices of the Charity Organization Society. The committee is composed of a number of prominent physicians and laymen and its objects are as follows: 1. Research into the social, as distinct from the medical, aspects of tuberculosis. 2. Education of the general public as to the prevention and curability of tuberculosis. 3. The encouragement of movements for suitable public and private sanatoria, for advanced and incipient cases, for adults and children. 4. The relief of indigent consumptives by the provision of suitable food and medicine. The work of the committee is not intended to be temporary merely, but its continuance and effectiveness will depend upon the public encouragement and support received.

The United States Government has done excellent work in its two sanatoria under the supervision of the United States Marine Hospital Service, the one at Fort Stanton for tuberculous sailors, the other at Fort Bayard for tuberculous soldiers. Both are situated in New Mexico.

Unfortunately the same department, upon the advice of the surgeon-general, has declared pulmonary tuberculosis a dangerous contagious disease, on the strength of which the Immigration Bureau excludes tuberculous visitors and non-pauper immigrants from our shores. The result of this declaration, backed by the United States Government,

has had already its unfortunate sequelæ. It has created an official and private phthisiophobia with the natural results of hardships imposed upon the consumptives, their friends, and their families. The New York Academy of Medicine has protested against such unscientific and inhumane procedures in adopting, at its regular meeting of February 6th, 1902, the following resolutions, which were submitted by the writer of this article:

"*Whereas*, The Treasury Department of the United States, upon recommendation of the surgeon-general of the Marine Hospital Service, has recently decided to classify pulmonary tuberculosis with dangerous contagious diseases. Be it

"*Resolved*, That the New York Academy of Medicine deeply deplores this decision, which is not based either on clinical experience or on scientific experiments;

"*Resolved*, That the Academy considers the exclusion of non-pauper tuberculous immigrants and consumptive aliens visiting our shores, unwise, inhumane, and contrary to the dictates of justice.

"*Be it further Resolved*, That, while the Academy is convinced of the communicability of tuberculosis and urges all possible precautions against the spread of the disease occasioned by sputum and tuberculous food, the Academy is opposed to all measures by which needless hardship is imposed upon the consumptive individual, his family, and his physician."

It is to be hoped that soon a wiser, more just, and scientific ruling will prevail, for in the light of our present knowledge pulmonary tuberculosis is not a dangerous contagious disease, but only a communicable one. To be in contact with a tuberculous individual who takes care of his expectoration or other secretions which may contain the bacilli is not dangerous. In sanatoria for consumptives, where the precautions concerning the sputum are most strictly adhered to, one is perhaps safer from contracting tuberculosis than anywhere else. The great danger from infection lies in the indiscriminate deposit of sputum containing the bacilli, which, when dry and pulverized, may be inhaled by susceptible individuals and then cause the disease to be developed. The communication of the germ of the disease is, however, less obscure to us in its process, and far more easily guarded against, than the contagion arising from such maladies as diphtheria, scarlet fever, or smallpox. The contact alone of a consumptive does not convey the disease; herein lies the difference between communicable and contagious. Therefore to consider the careful, conscientious consumptive an individual afflicted with a dangerous, contagious disease is unscientific, unjust, and inhumane.

Pauper immigrants should not be allowed to land, whether tuberculous or not; but there should be some discrimination when well-to-

do tuberculous immigrants or foreign consumptive visitors come to our shores.

The sanitary measures concerning tuberculosis in the various States in the Union I have tried to ascertain with the greatest possible accuracy by addressing the following questions to the respective State boards of health:

1. What laws and regulations exist in your State to combat the spread of tuberculosis (pulmonary or other)?

2. What recommendations, ordinances, circulars, public notices, etc., has your honorary board issued with the same purpose in view?

3. What sanatoria, special hospitals, and dispensaries for the exclusive treatment of tuberculosis, private or public, for adults or children, exist in your State?

4. What measures, laws, or regulations exist in your State to combat bovine tuberculosis?

On May 1st, 1902, answers from nearly all the State Boards of Health had been received. The following is a summary of the replies: Of 47 States and Territories only 10 have special laws to prevent the spread of tuberculosis from man to man; mainly, antispitting laws. Twenty-six States issue circulars for public instruction. Fifteen States report having one or more special institutions for the treatment of consumption. Twenty-five States reported having laws to combat the spread of bovine tuberculosis.

If this report teaches anything it shows the necessity for united federal action in the combating of so widespread a disease as tuberculosis.

To conclude this supplement we must finally mention the most important periodicals devoted exclusively to the subject of tuberculosis. The greater number of them have appeared during the last two years. *Die Zeitschrift für Tuberkulose und Heilstättenwesen* publishes articles and reports in English, French, and German, and is edited by Profs. B. Fränkel, C. Gerhardt, and E. von Leyden, and has about forty collaborators in various parts of the world. It is published in Leipsic by Johann Ambrosius Barth. In France there are *La Revue de la Tuberculose*, edited by Professors Bouchard, Chauveau, and Lannelongue; *La Tuberculose Infantile*, edited by Derecq and Barbier; and *La Lutte Antituberculeuse*, edited by Sersiron and Dumarest. The *Revue Belge de la Tuberculose* is edited by Dr. Van Ryn of Brussels. The English periodical *Tuberculosis* is the organ of the English National Association for the Prevention of Consumption. It is published in London at the central office of the association, 20 Hanover Square. In Germany appears the *Hygienisches Volksblatt*, with a special department for tuberculosis as a disease of the masses. In Buenos Ayres there is a Spanish periodical called *Revista de la Tuberculosis*, edited by Dr. Emilio R. Coni. In the United States we have the *Journal of Tubercu-*

losis, edited by Dr. Karl von Ruck, of Asheville, N. C. On April 1st of this year (1902), *Tuberculosis*, the official organ of the International Central Bureau for the Prevention of Consumption, a monthly publication, edited by F. Althoff, B. Fränkel, C. Gerhardt, E. v. Leyden, and G. Pannwitz, made its appearance.

With such an array of periodicals and journals, devoted exclusively to the spread of knowledge in the combat against tuberculosis as a disease of the masses, and in view of the widespread interest which, in common with the medical profession, governments, statesmen, philanthropists, and the people at large are now taking in the tuberculosis problem, well may we hope for the total eradication of the "great white plague" long before the "Twenty-first Century Practice of Medicine" shall have been issued. All that is required to attain this goal is the combined action of a wise government, well-trained physicians, and an intelligent people.

MALARIA.

BY

ETTORE MARCHIAFAVA

AND

AMICO BIGNAMI,

ROME.

Etiology.

Biology of the Malarial Parasite.—Since the publication of our article in Vol. XIX. there have been no researches made which modify or add anything of importance to the ideas then given out on the biology of the malarial parasite in man or mosquito. So that upon this subject we may be brief. We would, however, call attention to the various forms of nomenclature adopted by different authors to describe the various life phases of the parasite. Grassi, in his latest work, adopts the nomenclature used by Haeckel in his description of similar organisms. Parasites are reproduced in man by non-sexual generation (parthenogenesis), which has been called monogonia; in the Anopheles they are reproduced by sexual generation, or amphigonia. These two forms alternate regularly—cytometagenesis. The process of monogonia, to which is due an indeterminate number of generations developed in man in regular correspondence with the febrile attacks, has up to the present time been called "multiplication by sporulation," and very recently by a few authors, "multiplication by conitomic sporogonia or conitomia," *i.e.*, "multiplication by pulverization." Schaudinn proposes the term "schizogonia."

Multiplication by amphigonia occurs by successive direct divisions of the nucleus, or by conitomic sporogonia or conitomia; morphologically the process is similar to that of the parasites belonging to the monogonic cycle in man. Some hold with Schaudinn that the term sporogonia should be reserved for the anophelic cycle, using the term "schizogonia" for the human cycle.

The parasites originating by sporogonia conitomica in either man or Anopheles may be called sporozoites. Some, however, with Schaudinn, reserve this term for those originating in the Anopheles, and

this is the nomenclature adopted by us in this article. Following Schaudinn, however, parasites of the human cycle produced by schizogonia are called merozoites, instead of spores, as used to be the case. Parasites produced by fission in man are called monontes, to distinguish them from those produced by sexual generation, which are called amphiontes. Schaudinn calls the mononte, schizonte, and amphionte the copula, oökinete, and oöcyst. Some monontes are transformed in man to gametes (crescents, flagellate bodies, etc.). The macrogamete of Schaudinn (or the female) is called macrospore or oöide by Grassi, following Haeckel, and the microgametocyte of Schaudinn (flagellate body) is also called anteridium. The synonyms may thus be tabulated:

Haeckel-Grassi.		Schaudinn.
1. Monogonia (neutral generation by conitomic sporogonia or conitomia)		Schizogonia.
2. Monontes		Schizontes.
3. Sporozoites (monogonic)		Merozoites.
4. Macrospores	Gametes.	Macrogametes.
5. Anteridia	Gametes.	Microgametocytes.
6. Microspores or spermoids	Gametes.	Microgametes.
7. Amphigonia (sexual generation by conitomic sporogonia or conitomia)		Sporogonia.
8. Amphionte (vermicular when motile)		Copula, oökinete, oöcyst.
9. Sporozoite (amphigonic)		Sporozoite.

The most recent clinical, epidemiological, and parasitological observations unite in maintaining the classification of the parasites into three distinct species—quartan, tertian, and estivoautumnal.

As to the zoological nomenclature of these three species, Grassi in his latest work replaces the names formerly used by him and by Feletti with (1) plasmodium malariæ (quartan); (2) plasmodium vivax (tertian); (3) laverania malariæ (estival). It will be noticed that the name plasmodium, proposed by Marchiafava and Celli from the beginning of their researches, is now adopted by very many, if not by the majority of authors. A more important fact is that the theory emitted by us in 1892, namely, that the estivoautumnal species includes several varieties or sub-species, is being generally adopted. We were led to this conclusion by the fact that in estivoautumnal fevers we find a typical tertian with prolonged attacks (malignant tertian) and a quotidian, besides a variety found in the tropics. Even Grassi divides this kind of parasite into mitis and immitis. We do not absolutely indorse his nomenclature, since it has not been demonstrated that the parasites producing quotidian fever deserve the name of mitis. In support of this view we have the recent researches of Craig in the Philippines, showing that there is a quotidian type of fever due to the estivoautumnal parasites. Since the zoological nomenclature is constantly

changing, we shall cling to the one which best recalls the clinical types with their corresponding parasites. Plasmodium will apply to all three species, leaving aside laverania, which has been used with various significations, and the retention of which would only cause confusion. The following is the nomenclature which we suggest and adopt:

1. Plasmodium quartanæ (produces quartan fever).
2. Plasmodium tertianæ (produces tertian fever).
3. Plasmodium malignum (produces the estivoautumnal, the pernicious, and the tropical fevers, and is in close relation to hæmoglobinuria (including that from quinine). This probably includes several species, especially those of the quotidian and prolonged tertian.

The Seat of Development of the Plasmodium and of Hæmosporidia in General.—We have always held that the plasmodia are endoglobular and non-adherent to the red corpuscles. Recently several writers have sustained Laveran's theory that the parasites are only adherent to the erythrocytes.

Monaco and Panichi studied the action of an aqueous solution of quinine on various kinds of malarial parasites *in vitro* and observed that the parasites became detached from the red corpuscles. From the fact that the parasites execute no amœboid movements, these authors conclude that they do not make exit from the corpuscle, but are simply detached from it; hence that they are not endoglobular. Capogrossi, in Bignami's laboratory, has noted that the parasites leave the red cells only when hypotonic solutions (whether containing quinine or not) are added to the blood. Under these conditions rapid decoloration of the corpuscles accompanies the withdrawal of the parasite. Careful observation shows that the parasite slips out of the cell, being in reality pushed out by the escaping contents. It is a passive exit due to the increase in the contents of the red cell which is the effect of the penetration of the solution, hypotonic as regards the cell plasma.

Argutinsky, who followed Romanowsky's method of studying the blood, also holds that many parasites are merely attached to the erythrocytes. His sketches, showing that a portion of the parasite is free from the cell, are the same which we used to show the parasite at the moment of its entrance into or exit from the corpuscle.

In further support of our theory, we add the fact that in the blood of patients who have died of pernicious malaria, the dead young, non-pigmented parasites become round and remain within the corpuscle for several days. In fact, the parasites may be seen to move within the cells and rebound from one part of the periphery to another whenever the red cell is suddenly checked in its progress in the currents which are established in the specimen under observation. This could not occur if the parasites were not endoglobular. If they were merely ad-

herent to the corpuscle, they would become detached when their vitality ceased.

A study of the development of crescent bodies also tends to prove that the plasmodia are endoglobular, as in every stage of their growth they are always found surrounded by a stratum of globular substance. When the young ovoid bodies become elongated they drag with them the peripheral stratum of the corpuscle, the diameter of which is notably smaller than the largest diameter of the crescents and of the adult fusiform bodies.

Further support is derived from the study of the hæmosporidia of birds; proteosoma developing within their erythrocytes usually occupy one extremity when young, but gradually by their growth invade its substance and displace its nucleus. This could not happen were the proteosoma merely adherent to the red cell.

The young plasmodia at first adhere to the surface of the corpuscle, which they then push in, like a glove finger, at which stage a portion of their bodies appears free; changes next occur in the outer strata of the corpuscle, which allow of the entrance of the parasites, which become endoglobular and remain so until the corpuscle bursts and frees the monogonic sporozoites (or spores).

Origin and Significance of Crescents.—These bodies have been and still are the subject of numerous controversies and theories, although we do know one thing with certainty in regard to them, and that is that they are the starting-point of the anophelic cycle. Following Bignami and Bastianelli we hold and have had ample proof that the crescents originate chiefly, if not altogether, in bone marrow, where they may be found in every stage of development, whereas in other organs we find only a few young crescents or none at all. In spite of all opposition, this theory is unassailable. The fact that a few young crescents are sometimes found in the spleen or in the peripheral circulation does not invalidate our claim that bone marrow is their chief seat of formation and growth, and that in that situation monontes are transformed into gametes. It seems to us that the formation of gametes is a constant form of development in the life cycle of the parasites, rather than that it is connected with the relative immunity acquired after a certain number of febrile attacks, as held by Koch. Given a certain number of parasites, if many of them change to gametes, there will be a diminution of those multiplying by schizogonia, and a consequent attenuation of the infection. Yet if the parasites continue to multiply there may be an aggravation of the disease. Quinine given in small doses sometimes seems to increase the number of crescents; this is because the infection is gradually attenuated by arresting the development of some parasites which would have undergone multiplication by schizogonia, and this gives time for the development of the

gametes. Large doses of quinine arrest the growth of the monontes and act on the adult gametes.

We have always held that crescents represented a sterile form in man. Several authors, among them Grassi, believe that crescents multiply in man by parthenogenesis, which would account for the phenomenon of relapses after long intervals. There is no proof to sustain this theory. Moreover, in many cases of relapse no gametes are to be found in the splenic juice.

The Life Cycle of Fecundated Macrogemetes (Amphiontes) in the Anopheles.—In the first phase of this cycle in the intestine of the mosquito, the amphionte is transformed into the vermicule (oökinete of Schaudinn) endowed with motion; in the second the vermicule penetrates into the musculoelastic tissue of the intestine, and after rupture of the capsule the sporozoites are dispersed throughout the body of the Anopheles. We hold that in the intestinal wall the sporozoon surrounds itself with a capsule of its own. Grassi contends that an amorphous capsule is furnished by the intestinal muscular coat, because the parasites never detach themselves from this wall, because the capsule is continuous with the wall and gives the same reactions to coloring agents, and because the thickness of the capsule does not increase with the growth of the parasite, and in every stage remains transparent. All these phenomena we explain by the fact that we have found two capsules, one of which belongs to the parasite and the other is an external one furnished by the muscle tissue.

We have already stated that the size attained by the mature parasites varies greatly; and this even in Anopheles which have bitten only once, and in which we might expect to find the parasites all in the same stage of development. In the same stage of development, however, they may be of different sizes. Nor has this difference in size any relation to the number and crowding of the parasites within the Anopheles. This is in marked contrast to the regularity of the parasitic life cycle in man. The variability in development is in relation to the temperature of the surrounding atmosphere, and probably to the changes in temperature which occur between day and night. It is very probable that the time required for an anopheles to be able to infect a man after having been infected by a malarial subject is longer than the period of six to eight days required for an anopheles kept in the laboratory at a temperature of 30° C. The number of sporozoites formed by one amphionte is also variable. Grassi estimates that it may be more than ten thousand.

Owing to the extreme minuteness of the object of our study it is difficult to follow the formation of the typical sporoblasts; nor can we distinguish in the amphionte a stage of growth and one of reproduction. Nuclear reproduction begins in the first stages of development.

The nuclei multiply by direct division, the cytoplasm around each being gathered in irregular masses separated by fissures, vacuoles, etc. Partially distinct sporoblasts are thus formed, called by Grassi sporoblastoids. The nucleus of each sporoblastoid divides into a number of tiny nuclei which arrange themselves at the periphery of each sporoblastoid, and become surrounded by a zone of cytoplasm so as to form small cells from which the sporozoites (sporozoitoblasts—Grassi) originate. These sporozoitoblasts elongate and become sporozoites, one of their extremities remaining attached to the residual mass, but becoming separated later. The residual mass diminishes as the sporozoites mature; it is seen to be irregular, anfractuous, and furrowed with seams and cracks. From it may arise the brown or yellowish bodies of Ross. We do not yet know how the sporozoites, scattered through the body of the mosquito after the rupture of the capsule, finally penetrate into the salivary glands, but the process is undoubtedly an active one. Stephens and Christophers found that sporozoites taken from the salivary glands of Anopheles and placed in a salt solution in a room at 26.5° C. (79.7° F.) showed active movements for several hours. In normal human serum they became agglutinated, and also in serum diluted with a physiological salt solution in the proportion of 1:5. In the serum of persons exposed to continual inoculations agglutination occurs with a dilution of 1:15. In solutions of blood serum kept at 35° C. (95° F.) for twenty-four hours many sporozoites become annular, and when stained look like small circles of chromatin around a clear central area.

The Development of Quartan Parasites in the Anopheles.—The negative results obtained by experimentation with this parasite led us at first to conclude that Anopheles claviger might not be its preferred host; but we abandoned this theory on consideration of the fact that tertian and quartan are nearly always found in the same locality, and because in many of the places where quartan abound, only the Anopheles claviger is found, or at most a few individuals of A. bifurcatus. Further experimentation showed that Anopheles could not be infected from cases of recent quartan infection; but that they were infected by biting patients who had suffered from quartan fever for more than a year. Quartan parasites go through the same life cycle as the tertian and crescents. The many negative results obtained in experimentation are due to the great scarcity of gametes in the blood of quartan-fever patients. This also accounts for the rarity of quartan fever.

The temperature necessary for the development of the quartan parasite appears to be the same as for the tertian and that of the estival parasite.

The Malarial Mosquito.—All researches carried on during the past

three years confirm the fact that mosquitos of the genus Anopheles are the propagators of malaria, and this applies to all the species. In temperate climates *A. claviger* and *A. bifurcatus* are of chief importance. *A. variopinctus* is chiefly responsible for the spread of malaria in tropical regions.

While all recent investigations have confirmed the statement that wherever there is malaria there are Anopheles, the opposite has not been proved, *i.e.*, that the distribution of the Anopheles coincides with the distribution of malaria. Nuttall, L. Cobbett, and T. Strangeways-Pigg reached the following conclusions from their researches: (1) The disappearance of malaria from England is not due to the extinction of malaria-bearing mosquitos. (2) *A. maculipennis*, *A. bifurcatus*, and *A. nigripes* are found in districts which were once malarial as well as in non-malarial districts. (3) The disappearance of malaria is due to improved drainage, the reduction of the population in malarial districts, and the general use of quinine.

In Italy Celli and Gasperini pursued researches in the Tuscan Maremma, in which there are Anopheles, but no malaria. People fall ill there from fever acquired in neighboring localities, as Sardinia, who might infect the mosquitos, but the fact remains that autochthonous malaria does not occur. It is evident that the Anopheles are more widely disseminated than used to be supposed. In our original article we gave the *A. bifurcatus*, *villosus*, *nigripes*, and *claviger* as the malaria-bearing mosquitos, and of the spotted variety the *A. pictus*. Ficalbi in his latest work states that *A. villosus* and *nigripes* are varieties of *A. bifurcatus*.

Of the spotted Anopheles there are due species, *A. pseudopictus* and *A. superpictus*. Ficalbi now holds that the large spotted Anopheles of Italy is identical with *A. pictus* Loew. It is found all over Italy, but is apparently not so common as *A. claviger*. The habitat of the larva is the marsh, that of the winged insect, the woods. Some are found in houses. The female is extremely bloodthirsty and bites even in the daytime. *A. superpictus* is found in meridional Italy, and is malaria-bearing.

Experimental Infection of Man by Means of Malarial Mosquitos.—The experiment conducted in Rome on A. Sola was the first proof of the inoculation of man by malarial mosquitos. Those who raise the objection that the operation was not convincing because Rome is a malarial locality, do not realize that the hospital of Santo Spirito is in an absolutely non-malarial spot, and are ignorant of all the precautions observed. Manson's more recent experiment deserves wide recognition. Anopheles developed in this hospital were infected with a pure tertian and sent to London, where they were allowed to bite two volunteer subjects, Mr. Thorburn Manson and Mr. Warren. Both had

tertian fever, and in spite of quinine treatment Manson had a relapse after a period of latency of about nine months.

The Passage of the Malarial Germ from Mother to Fœtus.—Our conclusions that congenital malaria has not as yet been demonstrated have been confirmed by the recent researches of Ferroni carried on in Pavia (1902). He finds moreover that, as Bignami stated, the child is not specially influenced by the change in the mother's blood.

General Pathology.

Malarial Anæmia.—The recent studies of Dionisi show that it is not possible to state at what period of the disease there is the greatest destruction of red blood corpuscles. He ascertained that during the course of the fever and a few hours later, there is an oscillation in the number of red cells, in relation with the distribution of the blood, so that a few hours after the attack we may be able to estimate the grade of oligæmia produced by the attack itself. These oscillations are more marked in the more severe forms of malaria. Another point of interest is that toward the end of the attack there is a slight, transitory hæmoglobinæmia. With this last conclusion, however, we cannot fully agree, but hold that the pigment is increased rather than the hæmoglobin, as shown by the researches of Rosin and Jellinet.

In regard to variations in density of the blood (see Vol. XIX., page 193), Viola holds that in spite of all other influences these variations are in relation chiefly to the destructive action of the parasites on the one hand, and to the compensating action of the hæmatopoietic organs on the other. Dionisi, however, finds that a number of factors influence the density of the blood and hence the globular contents during the course of the fever; so that only the data obtained by an examination of the blood a certain length of time after the attack are of value in estimating the destructive action of the parasites.

The Production of Toxic Substances by the Parasites is a subject intimately connected with the question of the genesis of acute anæmia in malaria. Viola first advanced the theory that the destruction of red cells in malaria was due not only to the endoglobular development of the parasites, but also to the action of hæmolytic toxins. Marchiafava and Bignami also held that the estival parasites produced a toxin which caused early necrosis of the red cells. This opinion is gradually being accepted. Tripanosomata may be found in abundance in the red cells of birds without the production of anæmia, and again they may cause it, although situated outside of the corpuscles. However, these parasites are too far removed from the malarial parasite to give valuable data on the subject. Anæmia often persists long after the blood is clear of parasites, but this might be due to insufficient or slow

reparatory processes depending upon the condition of the bone marrow.

By the injection of malarial serum into healthy subjects, Celli, Carducci, and Casagrandi have found that it excites the hæmatopoietic organs, causing an increase of hæmoglobin and a more marked increase of red blood cells. This is an interesting fact, and we might reasonably conclude from it that the substances derived from the destruction of the red blood cells, and presumably to be found in malarial blood, are capable of exciting the new formation of red cells. These researches, however, have not succeeded in demonstrating the existence of a hæmolysin in malarial serum. Neither have laboratory experiments shown any marked hæmolytic action of malarial blood on healthy red cells.

No further progress has been made toward the demonstration of pyrogenous poisons produced by the parasites, which would explain the occurrence of fever at the moment of their multiplication. The fact that certain persons, especially of the more resistant races (as the negro) may have parasites in the blood without having febrile attacks, would seem to show the existence of pyrogenous substances of parasitic origin, in reference to which patients might acquire immunity.

The Agglutinating Property of Malarial Serum.—Lo Monaco and Panichi have found that the serum and the blood of patients affected with any kind of malarial parasite possess the power of agglutinating the red cells of other similar or different forms of malaria, and of healthy blood. The action is marked, and maintained even when the blood is diluted with a decinormal salt solution. It occurs in the later stages of the incubation period, is accentuated during the acute stage, persists after the last attacks, and ceases only with a complete cure. These authors attribute a decided diagnostic value to this sign, as does Grisconi. Ascoli, however, has found that the serum of normal individuals may feebly agglutinate that of other normal persons (although rarely), and that the same property is found in various other diseases. Capogrossi found this agglutinating property in many infective diseases, in nephritis, enteritis, etc., and especially in anæmia. The most agglutinating blood in malaria is that of cachectics. On the other hand, some malarial blood does not possess this power at all, or loses it when diluted with decinormal salt solution. Novi and Meruzzi also found that the blood of healthy but fatigued and fasting men could agglutinate normal red cells.

The result of the most recent investigations has greatly disturbed our faith in the diagnostic value of this sign. Lo Monaco and Panichi hold that the serum of malarial patients alone retains its agglutinating properties beyond a dilution of 1:5, which permits of a distinction between it and the serum in other diseases; but Capogrossi disputes this point, having found other serums which retain the power after strong

dilution. He finds, moreover, that the addition of quinine to decinormal salt solution does not alter the agglutinating property of malarial blood. All things considered, therefore, we have reached the conclusion that it is not possible by this sign to determine whether there is active or latent malarial infection, or whether the disease is cured.

We have so far referred to the phenomenon of isoagglutination (that produced by the serum of one individual upon the erythrocytes of another individual of the same species). There is besides the phenomenon of autoagglutination (that observed *in vitro* by serum on its own red corpuscles). In the case of some cachectics this has been found to occur in blood taken from the finger; Bignami observed it in cases of hæmoglobinuria, and Pace found that in the serum of hæmoglobinuria induced by quinine the isoagglutinating power was increased and the autoagglutinating power was also present.

Immunity.—Nothing of especial value has been recently added to our knowledge of the real nature of congenital or acquired immunity from malaria. Koch has found that in Java, in the most malarial regions, the disease may be regarded as one of childhood. On the coast of Kaiser Wilhelm's Land nearly all children under two years of age have parasites in their blood, and the number goes on diminishing up to fifteen years, few however being found after the age of five. The same circumstances obtain in the Bismarck Archipelago and in the Tami islands. This proves that there is susceptibility to the disease, but that immunity is acquired by slow degrees. Even the latent cases, however, may transmit the disease, as the blood in these cases contains gametes that are capable of being developed in mosquitos.

On the west coast of Africa A. Plehn (1901) did not find an absolute immunity among the negroes, but a relative immunity, by which he means that malarial attacks may occur under special conditions, as an intense infection, which, however, is attenuated in the individual.

Persons not suffering from malarial attacks, but with parasites in the blood, and suffering from anæmia, cannot be called absolutely, but only relatively, immune. In negroes the disease is apt to be cured after one or two attacks, without treatment, the symptoms are not severe, and fever occurs only after some special cause, such as traumatism. Plehn notes that in tropical countries the physicians are apt to administer quinine before performing important surgical operations, in order to avoid the post-operative occurrence of malarial fever. In Kamerun he found the greatest number of parasites in the blood of children, but they were also present in about fifty per cent. of robust adults. He holds that the relative immunity of the negro is congenital (differing in this from Koch), because infants frequently have the parasites without the disease. But the natives who have the disease in childhood certainly do not become absolutely immune, since they

not only often have parasites in the blood, but frequently have enlarged spleen. Plehn therefore concludes that in Africa there is a relative immunity from malaria, no stronger in adult life than in childhood, and hence congenital. It is very variable and may under certain conditions be lost.

We may infer from all this that in regard to malaria the African race differs from the European only in a greater congenital power of resistance, while as to acquired immunity all races would behave in about the same way. Koch admits the possibility of complete acquired immunity, which Plehn, however, does not grant. We have nothing to add to what we have heretofore stated in regard to relative immunity acquired by Europeans after they have long suffered from malaria. It would seem that birds infected by proteosoma may acquire complete immunity, as shown by some interesting experiments conducted by Pfeiffer.

The Genesis of Relapses.—This is one of the most obscure questions in the pathology of malaria. Relapses usually occur with a certain degree of regularity. For instance, patients who take only just enough quinine to check the fever and then stop using it, are apt to have a relapse in about fourteen days, an interval corresponding to the incubation period of a primary infection. Not rarely relapses occur at intervals of a month. Only recently it has been ascertained that after long periods of latency the relapses occur at certain seasons, and apparently according to some rule. A tertian may remain latent all winter and recur in the spring. An estival fever may disappear during the winter and spring and return in the summer. Many examples of this might be given.

Martirano and Ascoli hold that these relapses of estival fever after long latent periods are a regular phenomenon occurring in many cases, due to deposits of gametes which infect the Anopheles producing the new attacks, and thus initiating the new year of infection. For our own part, all that we can positively assert is that relapses do occur at the beginning of the epidemic year after a long period of latency, but we cannot say whether these occur with sufficient regularity to be of importance from an epidemiological point of view.

As to the genesis of the relapses, we have already referred to Grassi's theory that the gametes multiply in man by parthenogenesis. Although this hypothesis has its supporters, we hold that not only is it not based on fact, but that it does not offer a satisfactory explanation of relapses. That it is not based on facts was shown by Bignami and Bastianelli in their studies of the behavior of crescent bodies in man. As to the explanation of relapses, that it is unsatisfactory is shown by the fact that in many cases of relapse no crescents can be found even in the spleen. In quartan fevers which are apt to return monthly,

it is extremely rare to find gametes. Is it likely then that a relapse would be due to precisely that form of parasite which is found in least abundance?

From the established facts we may conclude that some of the relapses are due to reawakened pathogenic activity of parasites which have been completing their life cycle in a regular manner for some time without causing fever. This may not infrequently be seen in quartan fever, and, as we have before observed, may be due to the fact that the patient has acquired a transitory immunity toward the febrigenous action of the hæmosporidia. Should this immunity, from any special cause, be suspended, the relapse will occur. Various investigators, Plehn especially, have recently observed such cases.

Another group of relapses appears to be due to the progressive development of parasites which have escaped treatment by quinine administered in insufficient amount. These parasites do not necessarily become increased in number. Many cases of tertian and quartan fever are seen which, when untreated, go on for months without aggravation, perhaps even becoming attenuated, the number of the parasites not only not increasing (in spite of the regularly recurring periods of multiplication) but actually diminishing. This may be explained by the fact that not all young cells survive and develop. From this point of view, the genesis of the majority of relapses would be substantially the same as that of the group of relapses of which we have already spoken. In other words, they would always be due to the presence of the ordinary parasites of the pyrogenic cycle, whether or not these were in sufficient quantity to be found in the blood.

Even if we accept this explanation, certain problems remain unsolved. We cannot, for instance, understand why relapses should occur in certain cases after the long-continued use of large doses of quinine. There is of course the possibility that the parasites are more resistant to quinine during the period of latency than during the period of the attack. The practical result of experimentation is that the earlier quinine is administered in malarial infection the greater the chance of overcoming the disease, patients who have long suffered from malaria being more rebellious to treatment. Neither does the theory, given above, explain the succession of relapses occasioned by the various forms of parasites in mixed infections. For instance, a series of estivoautumnal relapses occurring during the autumn and winter and appropriately treated, will be followed by a relapse of ordinary tertian in the spring. Why should the tertian parasites have resisted the action of quinine to which the estival parasites succumbed, if they were in the blood in lesser number in the known forms of the pyrogenic cycle? Bignami holds that certain spores (monogonic sporozoites) are deposited during each attack in the viscera where they be-

come covered with a membrane and changed into resistant forms, thus becoming the source of future infections. This hypothesis would account for many of the circumstances above mentioned, especially the fact that the less severe and obstinate are the attacks the less likelihood there is of relapses. In concluding this part of the subject, we believe it possible to assert:

(1) That relapses are not in relation to the persistence and the parthenogenic increase of the gametes. (2) That in all probability relapses should be divided into two groups, in the first of which the parasitic substance which keeps up the infection during the period of latency consists of a minimum quantity of parasites of the ordinary pyrogenic cycle, which for a long time may not attain to a number or a virulence sufficient to cause the fever. In the second group the causative parasites are resistant forms originating from monogonic sporozoites deposited in the viscera during attacks which have not been treated with a sufficient amount of quinine. The first genetic mechanism is sustained by facts; the second is hypothetical, but we adopt it because of the difficulty of explaining all the circumstances by the first.

Clinical Notes.

Estivoautumnal Tertian Fever.—All recent writers agree to the accuracy of our description of this form of fever, but some object to the name which we have given it. Baccelli and Golgi propose the substitution of the name biduous fever for malignant tertian, in view of the length of the attacks. It is, however, the interval between attacks which has always served as guide in the nomenclature, wherefore tertian, or at the most biduo-tertian, should be the accepted term. Koch calls it tropical fever, and says that the term estivoautumnal does not apply in tropical countries, and that if this is called malignant tertian that of temperate climates should be called benignant tertian, which would be confusing. Our answer to the first objection is that tropical fever would not be a suitable name for temperate climates, where in many localities it exists in the summer and autumn, nor would it be suitable for the tropics, where the other kind of tertian also exists. As to the second objection, we confess ourselves unable to perceive any possible confusion to be caused by applying the term benignant to ordinary tertian and malignant to the form which may become pernicious. On the contrary, it would tend to clearness. Therefore we cling to our name of estivoautumnal or malignant tertian. Bignami has recently seen cases of the type of fever, described by us, in which the attacks are separated by intervals of about thirty-six hours. It may be considered a variety of malignant tertian, but we shall continue to call it subtertian.

Quotidian Estivoautumnal Fever.—It is a disputed point whether there is a true quotidian fever due to estivoautumnal parasites or not. R. Koch denies the existence of a true quotidian, and holds that it belongs to the type which we call estivoautumnal tertian, and signifies merely a relapse. This theory would exclude all belief in a variety of parasite causing a true quotidian, a belief which we have held, but with some reserve to be sure. Quotidians tend to relapse as quotidians and tertians as tertians. Recent researches tend to prove the existence of a true quotidian. Caccini, studying estivoautumnal fevers, not only has seen the quotidian type repeated in relapses, but by inoculating healthy individuals with this blood has reproduced a distinctly quotidian fever. As it has already been demonstrated that inoculation with estivoautumnal tertian blood produces estivoautumnal tertian fever, Caccini's experiments demonstrate the existence of two varieties or distinct sub-species of the estivoautumnal parasite. This we stated in 1890. Positive proof will be obtained only when gametes infected with true quotidian parasites reproduce the same type by the inoculation of a healthy individual. Craig in the Philippines has studied the same kind of fever and asserts that the quotidian is a distinct clinical type.

The Pathogenesis of Pernicious Symptoms, Especially the Nervous Syndrome of Malarial Origin.—As stated in our original article, the cerebral symptoms in pernicious fever are related to nutritive changes in the nerve cells of the brain,* secondary to circulatory disturbances, caused in their turn by parasitic changes in the red blood cells, and to lesions of the endothelium of the blood-vessels. Of late, objections have been raised to this view, and a tendency has developed to attribute all the phenomena to an intoxication, the parasites producing not only a pyrogenic, but a hæmolytic toxin, neurotoxic substances, etc.

As yet we cannot regard this theory as proved. We were among the first to attribute certain changes to the action of toxins, but changes in the cerebral circulation are certainly sufficient to account for some of the nervous symptoms, such as coma, transitory aphasia, hemiplegia, etc. Moreover, we hold that more weight should be given to *secondary intoxication* in malaria than to direct toxic action—in other words, to the toxic products derived from the cells which degenerate or become necrosed from parasitic invasion.

The nervous phenomena following acute infections are more difficult of interpretation, but are probably due to the secondary intoxications just alluded to. Alterations of the nerve cells produced by disturbed circulation should also be taken into account, as should be the

* By an error the observations on changes in the nerve cells, studied according to Nissl's method, were attributed to A. Monti instead of to Bignami.

fact that intoxications of other origin, such as intestinal, may complicate matters. Quinine may possibly act as a poison to the nerve centres when taken in large and long-continued doses. Schupfer holds that nervous heredity, syphilis, and alcoholism may play a predisposing part.

Schupfer holds to the theory of intoxication in these postmalarial nervous symptoms, while Pansini supports the theory which we have upheld. The former reports six cases in which the chief symptoms were disturbances in locomotion and bulbar symptoms. In one case the lesions presupposed peripheral as well as central lesions.

Pansini describes cases of pure cerebellar lesions. The result of these investigations appears to be that the symptomatology of these malarial nervous diseases is multiform, but that in many cases there are cerebellobulbar symptoms. Resemblances to definite nervous diseases (as multiple sclerosis) are merely superficial.

Schupfer has studied two cases of malarial polyneuritis which were characterized by motor and sensory disturbances during the febrile attacks, the rarity of reactions of degeneration in the paralyzed muscles, the frequency of vasomotor and trophic changes, and the absence of disturbed sphincter action. Symptoms of multiple neuritis may accompany cerebral or cerebellar symptoms. Nothing is known as to its pathogenesis, but one is naturally led to suppose that an intoxication is secondary to or complicates the malaria.

Malarial Hæmoglobinuria.—Quinine is being more generally recognized as a causative factor in this condition, though we are not ready to admit that it is always the cause. It is still a disputed point whether hæmoglobinuria in all its forms is related to any special form of malaria or not. We in Rome have attached the chief importance to estivoautumnal fever because we have seen the symptom only in these cases, while it is well known that it is chiefly met with in regions where this form of infection predominates. We also hold to the idea that a special form of parasite creates a predisposition to hæmoglobinuria. Sambon and Manson hold it to be due to a parasite differing from the kind pathogenic to man, and probably similar to the Pyrosoma bigeminum which causes the Texas fever in cattle. This theory is not sustained by the facts observed. Moreover, in cattle, the hæmoglobinuria is in direct relation to the intensity of the infection, whereas in man this relation does not exist, and hæmoglobinuria may occur, whether from quinine or not, even when there is no actual malarial infection.

Another much discussed point is whether hæmoglobinuria occurs only in patients with estivoautumnal or tropical fever. Out of forty-one cases Koch claims to have seen five in which this condition occurred in ordinary tertian fever. In four of these cases reported at

length by him, it is our opinion that a mixed tertian and tropical malaria could not be excluded; in one of them indeed (Observation 12) this mixed infection was demonstrated.

In a case of our own we found tertian parasites during the attack of hæmoglobinuria, but there was a relapse with estival parasites which proved the mixed nature of the previous infection. In another fatal case in which during life only the parasites of ordinary tertian were found, the autopsy showed crescents in the spleen and in the bone marrow.

As to quinine hæmoglobinuria, many writers, among them Grocco and Vincenzi, and more recently Otto, have observed it during the course of a quartan fever. To conclude that the symptom may occur in any form of malaria appears to us to be unwarranted; in any case the chief importance attaches to estivoautumnal fever in relation to any form of hæmoglobinuria occurring during malaria.

As to the pathology of hæmoglobinuria, there is little to add to what we have already stated. The majority of investigators have studied the form produced by quinine, which is the most frequent and most important, as indeed Tomaselli recognized and asserted many years before Koch. The latter holds that hæmoglobinuria may occur after the use of quinine independently of any actual malarial infection. This had been already recognized by us (postmalarial hæmoglobinuria), by Murri, Vincenzi, and others. He admits an individual predisposition which may be hereditary (a fact already established by Tomaselli), due in his opinion to diminished resistance on the part of the red cells. Why there should be a diminished resistance is a mystery. Neither a tropical climate nor tropical malaria alone can be the cause. Koch attributes it to the combined action of many factors. Our own opinion is that this predisposition is due to a special variety of estivoautumnal infection.

The results obtained by Pace in a series of researches on the blood and the urine of patients during attacks of hæmoglobinuria and in the intervals are as follows: In the intervals: (*a*) The blood mixed with quinine *in vitro* remains unaltered by various salt solutions, behaving in fact like normal blood. (*b*) The blood in mass merely shows the signs of slight anæmia. (*c*) The serum *in vitro* exhibits no hæmolytic powers when in contact with the red cells of other individuals, not even when quinine is added. (*d*) The urine contains no bodies capable of dissolving the red corpuscles of the same person, or of a normal person, not even when quinine is added, whether the blood be taken during or between attacks.

During the attacks: (*a*) The blood cells, tested with salt solutions, show no deviations from normal resistance. Neither is resistance to mechanical injury diminished (Chvostek's test). (*b*) The dry residuum

and the ashes are diminished and the chlorides increased, as in many cases of anæmia. (*c*) Morphological examination of the blood reveals no changes of moment, and especially no shadow corpuscles are found. (*d*) The blood serum is of an ochre or of a golden-yellow color. The author has never found signs of hæmoglobinæmia during the attack. He supposes the color of the urine to be due to bilirubin, but has no absolute proof of this. (*e*) The isoagglutinating power of the serum is increased (toward normal red blood cells), and there is autoagglutinating power as well. No hæmolytic action on normal blood has been demonstrated. (*f*) Oxyhæmoglobin and methæmoglobin have been found in the urine. In aborted attacks there may be urobilin only. He has found no hæmolytic power in the urine, and holds that this power, when found, depends upon the chemical composition of the urine, especially upon concentration of its salts. These researches, while they confirm statements already made, do not solve the problem of the pathological mechanism of hæmoglobinuria. Not having observed hæmoglobinæmia during the attack, he concludes with Berthier that the hæmoglobinuria is of renal origin. But Murri, Grocco, and Bignami have found evidences of hæmoglobinæmia, and in any case its absence at a given moment during the attack does not prevent the fact that there may be a dissolution of the red cells in the circulation.

Bignami has recently studied two cases of quinine hæmoglobinuria, and has attempted to reproduce hæmolysis *in vitro*, by means of quinine. An interesting fact in connection with these experiments is that equal doses of quinine do not always produce the same effects. A recent infection appears to increase the sensibility toward quinine. The conclusions reached were that serum and globules taken from a patient suffering from quinine hæmoglobinuria, and treated with quinine *in vitro*, do not behave differently from the serum and corpuscles of normal persons or of malarial patients normal in respect to quinine, all of which tends to confirm the theory that quinine does not produce hæmoglobinuria by direct action on the cells or the plasma, but by action *in vivo* upon some special organism.

The negative results obtained by Bignami were easily foreseen, starting from his theories as to the origin of this form of hæmoglobinuria, previously stated. He holds that it occurs in the circulation from the action of two substances: one a "sensitizing" body or "antibody," due to the malarial infection, and one the "complement" due to the quinine. (These terms are used in the sense given them by Bordet and by Ehrlich.) The "antibodies" or immune bodies unite chemically with the altered red cells, just as in the case of the specific immune bodies (Ehrlich). When the "complemental" bodies are formed by the action of quinine, they combine chemically with the immune bodies and thus hæmolysis is produced. According to this theory

there is no hæmolysin free in the plasma, and therefore hæmolysis is not demonstrable *in vitro*.

Nearly all authorities agree that hæmoglobinuria is produced by two factors: malaria which gives the *predisposition*, and quinine which by its action on a special organism furnishes the *occasion* of the attack. Bignami merely puts this idea into concrete form. The "antibody" constitutes the predisposition, the "complement" the occasion. Many apparently contradictory phenomena may be explained by this hypothesis. For instance, while quinine is often the cause of hæmoglobinuria, its continued administration in such cases does not always cause an aggravation of the symptoms, and not infrequently recovery follows. Were its action simply that of an ordinary poison, the fact would be incomprehensible. But if the presence of an "antibody" is necessary to hæmolysis, and if this body is consumed during the process, the action of the quinine would of course become *nil*. This theory also explains why a subject who has recovered from hæmoglobinuria and lost his sensitiveness to quinine may again be affected by small doses of it after a relapse of malarial fever.

Some Complications of Malaria.—Typhoid Fever. As already stated, we have proof positive that malaria and typhoid fever may occur together. Cases have been reported from the United States, from India, Algeria, Italy, etc. Craig found the malarial parasite in the blood of patients suffering from typhoid fever, as shown by the presence of the Widal reaction and by the clinical features of the disease. Fiocca in Rome observed a relapse of malarial fever between the primary attack and a relapse of typhoid, the latter being followed by another relapse of malaria. Such alternation is rare. More frequent than cases of true complication are those in which one infection follows the other. One must be careful not to confound malarial fevers occurring after typhoid with intermittent fevers of typhoid origin which often occur during convalescence from this disease. While many observers report typhoid fever developing after the cessation of malaria, in our experience it is but seldom that it occurs with malarial cachexia. This is but an example of the well-known law that typhoid has no predilection for an organism weakened by some other disease.

Malaria and Cancer. In a recently published article, Löffler, reviving the theory of some of the older writers, holds that there is an antagonism between the two diseases, and suggests the treatment of cancer by means of injections of malarial blood. The chief support of this theory is the fact that cancer is unknown in intensely malarial tropical countries. This is doubtless a racial characteristic merely, for we in Italy have several times found cancer in malarial subjects. Nor have we any proof of antagonism between the two. We do not know whether there have been any attempts at the treatment suggested by Löffler.

Cardiac Disturbances.—In malarial patients there is sometimes a certain degree of cardiac dilatation, which may persist for some time after the attacks, and is probably connected with the acute anæmia. After subsidence of the fever marked bradycardia may be noticed; even in robust patients there may be only from forty to forty-five pulsations to the minute. Quite recently Gallenga has described a case of paroxysmal tachycardia and acute dilatation of the heart during a tertian fever in an alcoholic and possibly syphilitic patient. He considered it due to the action of a malarial toxin, but in so mixed a case we do not think it possible to state that it was other than a complication. In some cases we have observed symptoms of acute cardiac insufficiency with tachycardia, especially at the beginning of the malarial attack, and in persons with chronic cardiac lesions, particularly valvular ones.

The Action of Quinine.—We have already described the action of this drug *in vivo*. As to its action *in vitro* the reader is referred to the recently published report of Capogrossi's work done in Bignami's laboratory.

Lo Monaco and Panichi, finding from their experimentation *in vitro* that under the action of quinine the parasites make their exit from the red corpuscles (or become detached from the corpuscle, according to their theory previously mentioned), conclude that the same process occurs *in vivo*, and that the beneficial action of quinine depends upon the fact that the parasites fall into the plasma where the conditions are unsuitable to their life and development. Upon this theory they base a whole series of therapeutical deductions.

Capogrossi, however, concludes from his researches that the exit of the parasites is merely a physical result of the hypotonicity of the solution used by Lo Monaco and Panichi, and does not represent any specific influence of the quinine. He holds that quinine in an isotonic solution of sodium chloride does not act by causing an exit of the parasites from the red cells, but "determines an immobility on the part of the developing parasites, and sometimes induces in them certain changes which render them more opaque and sometimes give them a tint of hæmoglobin; or else a circumscribed yellow body surrounded by a clear halo (juice or nuclear chromatin) is visible in them." Similar results follow the addition to parasitic blood *in vitro* of a drop of blood serum obtained by bleeding from a patient who has taken a therapeutic dose of quinine.

Epidemiology and Prophylaxis of Malaria.

For years the study of malarial infection was pursued by a few scientists only, but at the present day a large number of investigators have taken up the subject and are endeavoring to solve the problems

so intimately connected with the welfare of the hosts of working people exposed to the disease. It seemed at first as if the discovery of the parasite and of the rôle taken by the mosquito had accomplished the desired purpose, but later the matter was seen to be less simple than was at first supposed. According to theory, about a month before the beginning of an epidemic there should be a number of persons capable of giving the infection to mosquitos. In point of fact, however, such cases were extremely rare. It was then supposed that a latent form of malaria existed, the sexual forms of the parasite remaining hidden in the organism. It was also observed that in the hospitals the greater number of sexual forms were seen in the autumn just as the malarial infection was at its ebb. Further investigations were pursued, with the best possible results. We now understand just how malaria is developed and are in a position to lead a crusade against the disease. Krumpholz has recently written: "The war against malaria costs money, as does all war; but our welfare does not cause misery and death to the victors, our battlefield is transformed into a flowering field in which health and well-being take the place of disaster and poverty." If not actually applicable at the present time, these words are certainly prophetic, for we are on the right road, and we have reason to hope that wise legislation will soon preserve our workers from all infection. The problems which have occupied investigators of late years have been the following: (1) To ascertain the general course of epidemics in various regions. (2) The annual course of the three kinds of malaria. (3) The annual course of the relapses of these three varieties, and the connection between them and later infections. (4) The relation of epidemics to the infection and the life of to Anopheles.

From the result of investigation we reach the following conclusions: (1) That the majority of Anopheles infected in the stomach and probably capable of infecting man are so infected at the height of the epidemic. (2) That Anopheles infected in the salivary glands are extremely rare during the decline of an epidemic. It is probable that many parasites are arrested in the first stage of their development, or degenerate. (3) The connection between the infection of the Anopheles and the first cases of estivoautumnal fever has not as yet been clearly demonstrated. (4) The ordinary tertian relapses very frequently in March and in April, and as a result Anopheles, which are very scarce at this season, are only exceptionally infected in Central and Southern Italy. There is an analogy between this occurrence and the fact that in October, although the gametes of estival fever are then very abundant, the Anopheles either do not become infected in proportion to the number of the parasites, or else the latter do not complete their life cycle within their hosts.

It can be definitely stated that malarial epidemics are in relation to increased temperature, which varies according to the region and the year, and that the decline of the epidemic comes with decreased temperature.

Prophylaxis.—The preventive measures used up to the present time have been: (1) Treatment of relapses with the double end in view of curing them and of limiting or preventing the infection of mosquitos. (2) Protection of the healthy against the development of parasites with which they have been inoculated by Anopheles. (3) Protection of malarial patients so as to prevent the infection of mosquitos. (4) Protection of healthy individuals from the bites of mosquitos. (5) War on the Anopheles in every stage of development.

The treatment of relapses has been tried by means of the salts of quinine, euquinine, and iron and arsenic, the aim having been to secure the disappearance of the parasites or to restrict their action. Adult gametes are not affected by quinine, which might occasion a doubt as to the good results of this method; but, on the other hand, everything leads us to think that the *young* gametes are influenced by the drug. A series of researches have given varying results, but from the totality of these we may conclude that the use of even large amounts of quinine will not prevent the development and extension of epidemics of fever. If its administration is greatly prolonged, however, with or without the contemporaneous use of iron and arsenic, there will be good results.

Another series of experimental treatment demonstrates the value of prophylactic medication on persons who have previously been cured of relapses by the methods given above as well as on the healthy.

For the protection of malarial patients to prevent infection of mosquitos, mechanical means have been extensively used and excellent results obtained.

War on the Anopheles has been carried on against the larvæ with chemical substances, more especially with petroleum poured over marshy places every three weeks, in the proportion of one litre to two hundred or three hundred square metres. Marras claims success with this method, but it is applicable to a very restricted area. The petroleum should be applied in the winter and spring. The destruction of larvæ has also given good results in the outskirts of Bologna.

We add here the text of the Italian laws and regulations for the prevention of malaria, from which great benefits are looked for. Credit for the initiative in this respect is due primarily to Celli, and also to Fortunato and Franchetti, who labored actively in support of these laws.

LAWS AND REGULATIONS DIRECTED TOWARD THE DIMINUTION OF THE CAUSES OF MALARIA.

ARTICLE 1.—The Minister of the Interior, after consultation with the provincial and national boards of health, shall by royal decree declare what districts in the kingdom are at present malarial, and note in future any changes which may occur in the same in this respect.

ART. 2.—In the regions so established, the farm laborers and others employed permanently or temporarily in any work with fixed wages or under contract, shall, when affected with malarial fever and when the charitable organizations are unable to provide for them, be gratuitously furnished with quinine by the several municipal administrations during the whole duration of treatment as prescribed by the communal physician.

The expenses incurred by each commune, after certification of the amount in the manner prescribed by the Regulations, shall at the end of each year be charged up against the landowners in the respective malarial districts, in proportion to the size of each estate. The amount so apportioned shall be published on the 30th of November in *The Communal Gazette*, and if fifteen days elapse without protest to the Communal Council, it shall become a legal charge.

ART. 3.—Laborers employed on public works shall, when stricken with malarial fever, receive gratuitous medical assistance and quinine either from the public administration conducting the work, or from the contractors, secured by taxes laid on the enterprise in the contract of agreement. Any contractor who fails to pay the above-mentioned tax shall be liable to a fine of from 100 to 1,000 lire. The moneys collected in this way shall be added to the fund called "Subsidy for the diminution of the causes of malaria," established by Article 5 of the law of December 23d, 1900, regarding the sale of quinine. Cases of death occurring from pernicious malarial fever, contracted in the public works, and proved to be due to the non-administration of quinine, by fault of either the public administration or the contractors, shall call for indemnity at the same rate as that established by the law of the 17th of March, 1898, in the case of casualties.

ART. 4.—The quinine referred to in Articles 2 and 3 of this present law shall be that furnished by the state.

ART. 5.—In the open country, in the malarial districts referred to in Article 1 of this present law, the premises occupied by custom-house officers, by employees on the national highways, whether provincial or communal, on the railways, or in the improvement of societies, and by contractors for public works, shall be protected against

the entrance of flying insects from the month of June until December. Landowners and manufacturers who will observe the same precautions in regard to the homes or the temporary abodes of the farm laborers and others shall, upon the recommendation of the provincial board of health, and after hearing of the committee of inspection, according to Article 8 of the law of the 23d of December, 1900, be awarded premiums up to the amount of 1,000 lire, to be taken from the fund derived from the sale of quinine.

ART. 6.—In malarial regions, in places where there is a sufficient slope for this purpose, landowners shall be obliged to facilitate the drainage of waters which might otherwise accumulate in stagnant pools in natural or artificial depressions in the soil. Contractors for the making of roads and canals shall, as far as possible, avoid all unnecessary excavations in which, when abandoned, water might collect and form stagnant pools.

ART. 7.—The execution of this law shall be provided for by regulations approved by royal decree.

Regulations for the Execution of the Law of November 2d, 1901, Containing Plans for the Diminution of the Causes of Malaria.

ARTICLE 1.—In the meaning of the Law of the 2d of November, 1901, a region may be designated as malarial:

(1) When several cases of malaria contracted in that place occur simultaneously or within a short space of time.

(2) When in connection with these cases of malaria there are present the flying insects recognized as capable of transmitting the infection, and also when there are, at a greater or less distance from habitations, stagnant pools or other collections of water, either permanent or temporary, large or small, artificial or natural.

ART. 2.—The provincial physician, so soon as he shall have learned, either directly or through a sanitary official, that cases of malaria have occurred in any given locality, shall take all steps necessary to ascertain whether the conditions mentioned in the preceding article are or are not present. In the affirmative case, he shall present his report at once to the prefect, and urge him to call a meeting of the provincial board of health.

ART. 3.—The provincial board of health shall, if necessary, make further investigations, and shall prepare a statement which, with that of the provincial physician, shall be forwarded to the Minister of the Interior and transmitted by him to the national board of health. The statements in the report should be accompanied by the necessary proofs, and should contain the data essential to the delimitation of the district declared infected.

ART. 4.—As a rule, a malarial district should be contained within

the territorial limits of the commune. The general government, however, has the power to include in one malarial district portions of two or more communes which are contiguous and belong to the same province, and which present the conditions described in Article 1 of these regulations, providing that this union of districts is demanded by special topographical conditions, or because the laborers residing in one commune are in the habit of repairing to the other commune or communes in search of work. In this event, the prefect, having consulted with the provincial administrative council, shall divide among the various communes, according to the area of each included in the affected territory, the total moneys held by the communal administrations for supplying quinine to the husbandmen and laborers, according to Article 2 of the law, and communal administrations later attending to its apportionment among the landowners.

ART. 5.—When for any reason a change occurs in the conditions under which a special region was designated as malarial, the rehabilitation of such region shall be effected through the same procedures as those observed for its condemnation.

ART. 6.—According to the law of the 2d of November, 1901, the term laborer applies: (1) To any one who permanently or temporarily, under regular wages or remuneration fixed by contract, is employed in any work. (2) To one who, under the same conditions, even without personally participating in active work, superintends the work of others, and receives daily or monthly pay therefor. (3) To the apprentice who, with or without pay, assists in the work. The obligation regarding the free distribution of quinine applies to every one employed on the estate who is in any way engaged in agricultural labor.

ART. 7.—In regard to the charitable societies and the public benevolent institutions under their control in the communes in which a malarial region has been declared to exist, the provincial administrative council shall see that in the budget in which an appropriation for the purchase of medicines for the poor is asked for, there is a distinct order for a sum to be spent yearly in providing quinine, according to article 2 of this present law. Such sum shall not be less than the average amount expended in the preceding three years for furnishing quinine to the sick poor.

ART. 8.—The gratuitous administration of quinine to the husbandmen and laborers shall be made directly by the communal administration to which, not later than December 31st of each year, the charitable society shall pay the sum referred to in the preceding article, upon presentation of a statement of the expenditure made. Such charitable societies, however, as possess the means to furnish all the quinine necessary for the husbandmen and laborers, shall provide it directly,

but the commune shall hold itself ready to assume the responsibility for expenses for the quinine at any time that the charitable societies are not in condition to do so.

ART. 9.—The communal physician who administers the quinine to the husbandmen and laborers, according to Article 2 of this law, shall at once furnish a copy of its receipt to the municipality, and also to the charitable society, should this be the source of the supply, giving the name and surname of the husbandman or laborer, as well as that of the person for whom such husbandman or laborer was working at the time when attacked by the disease. Before apportioning the amount to be paid by the landowners, the commune must deduct the amount to be reimbursed by the charitable society.

ART. 10.—Each commune, within the limits of which is contained a malarial district, shall keep an indexed list of the names of such persons as have received quinine, also preserving copies of the prescriptions given by the physician.

Liquidation of all expenditures shall occur in the month of December of each year, and be based upon the above-mentioned indexed list, certified to by the secretary of the commune and the mayor, and countersigned by the prefect.

ART. 11.—The payment of the moneys advanced by each commune shall be made by the owners of lands included in the malarial region, in proportion to the size of each individual property. The only persons to be exempt from this tax are: 1. Landowners who cultivate their own land, and do not either temporarily or permanently employ laborers. 2. The public administration which employs laborers exclusively for the execution of public works and which is already taxed as by article 3 of this present law. In the case of leasehold property, or land burdened with mortgage, the tax shall be paid by the tenant or incumbent.

ART. 12.—Should a husbandman or laborer who has contracted malarial fever when working in an infected district of a commune leave it to go to a non-infected district of another commune, the first commune shall, upon a medical prescription, give him sufficient quinine for continuation of treatment during the journey and for five days after reaching the new commune. A similar provision of quinine shall be given to such husbandmen or workmen who at the time of their departure do not exhibit the symptoms of a well-developed malaria, but who do show indisputable signs of a latent infection.

ART. 13.—Whosoever permanently or temporarily employs husbandmen or laborers in localities two kilometres or more distant from a licensed store or a pharmacy which, according to the law of December 23d, 1900, has undertaken the sale of quinine furnished by the

state, shall make a requisition on the municipality or the charitable society, as provided for in the preceding article, for an amount of quinine sufficient for three days' treatment for each husbandman or workman, to keep it on hand and to administer it when needed.

ART. 14.—No change is proposed in the existing rules relative to the sums allowed for the poor in the hospitals or other institutions, for the purpose of treatment in cases of disease or accident.

ART. 15.—In addition to reporting cases of malaria to the health officer, according to article 45 of the law of the 22d of December, 1888, physicians shall be obliged, under penalty, to report to the office of Public Safety of the commune any case in which the contractors of public works fail to meet the obligations imposed upon them by article 3 of the law in regard to gratuitous medical assistance, and the gratuitous distribution of quinine to laborers on public works who are affected by malaria. The directing engineers and the superintendents in charge of public works shall see that the contractors fulfil the above-mentioned obligations. In case of violation of these obligations by the contractors, the fine imposed by article 3 of the law may be exacted also from the directing engineers and the assistants.

ART. 16.—Societies which operate the railway systems belonging to the state are, as respects their employees, subject to the requirements of article 3 of this law, regarding the public administration and contractors.

ART. 17.—Any physician who shall have knowledge of a case of death from pernicious malaria contracted by a laborer while employed in public works shall report the case, and send a death certificate to the office of Public Safety of the commune. Should any doubt arise as to the diagnosis of death from malaria, the matter should be settled by autopsy.

ART. 18.—The methods of protection which, according to article 5 of this law, are to be provided for the premises occupied by the custom-house officers, by employees on the national highways, whether provincial or communal, on the railways, in the improvement societies, and by contractors for public works, shall by the respective administrations and contractors be applied to the doors, windows, or any other aperture communicating with the outer air, in such manner as to prevent the ingress of flying insects. The rules to be followed in the placing and working of such methods of protection shall be given by the Minister of the Interior.

ART. 19.—As a safeguard against the neglect of public administrations to fulfil the obligations treated of in article 5 of this law, administrators of directors of railways and contractors on public works who do not fulfil these obligations shall be liable to the penalties

imposed by article 50 of the laws of hygiene and public sanitation. The observance of these obligations shall be enforced by the police, by the national sanitary authorities, and by the officers of the railway administration. The administrations and contractors shall provide for the supplying and placing of the means of defence treated of in this article, within two months from the publication of the present regulations.

ART. 20.—The proprietors and manufacturers who, having provided protection for the houses of their workmen and peasants according to the preceding article, wish to compete for the premium treated of in article 5 of the law should, before the month of June, request the prefect to order an examination of the premises, that the methods of protection may be certified to as satisfactory. The prefect shall direct the provincial physician or some official of the civil government to make the examination and to send in a report of the same. The prefect shall assure himself that the methods of protection are maintained between the months of June and December. In the award of the premiums, other things being equal, preference shall be given to such proprietors and manufacturers as in addition to providing means of defence for the houses and shelters of their laborers, shall have also provided for the laborers and peasants means for the protection of their persons against the bites of flying insects.

ART. 21.—The making of any side excavations by the contractors for the building of roads and canals shall be only by license from the mayor of the commune, who, having taken counsel of the sanitary and engineering officers of the commune, shall give his consent only in cases in which a necessity for the same has been clearly demonstrated.

Should permission be granted, a time should be fixed for closure of the excavation and for such a restoration of the surface as will prevent the formation of any stagnant pools.

ART. 22.—Independently of the conditions which in relation to Article 6 of the law might in the case of rice culture in malarial zones be included in the provincial regulations treated of in the law of the 12th of July, 1866, there shall be offered premiums and other encouragements to all cultivators of rice who shall provide for and develop any methods which tend to further the free drainage of the soil.

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